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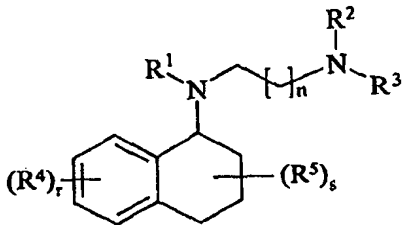

(I)

(57) Abstract

1,2,3,4–Tetrahydronapthalene derivatives of formula (I) wherein R^1 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and phenylC_{2-6}alkyl and R^2, R^3, R^4 and R^5 are as defined in the specification are described, together with processes for their manufacture and compositions containing them. Compounds of formula (I) are pharmacologically useful.

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1,2,3,4-TETRAHYDRONAPHTHALENES AND THEIR PHARAMACEUTICAL USE

Field of The Invention

The present invention relates to chemical compounds, in particular 1,2,3,4-tetrahydronaphthalenes, to processes for their preparation and to chemical intermediates useful in such processes. The present invention further relates to 1,2,3,4-tetrahydronaphthalenes, to pharmaceutical compositions containing them and to their use in methods of therapeutic treatment of animals including man, in particular in the treatment of neurological disorders.

Background

Neurological disorders, to which the present invention relates, include stroke, head trauma, transient cerebral ischaemic attack, and chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia.

Emopamil has classically been thought of as a neuroprotective agent whose efficacy is most likely derived from actions at either voltage-sensitive calcium channels (VSCC) or 5-HT_2 receptors. An apparent paradox to this logic is that verapamil, although chemically and pharmacologically very similar to emopamil, is not neuroprotective. While the lack of neuroprotective efficacy by verapamil was initially explained by lack of CNS penetration, recent studies suggest other factors may be involved (Keith et al., Br. J. Pharmacol. 113: 379-384, 1994).

[^{3}H]-Emopamil binding defines a unique high affinity site that is not related to VSCC, is found in the brain, but is most prevalent in the liver (Moebius et al., Mol. Pharmacol. 43: 139-148, 1993). Moebius et al. have termed this the "anti-ischaemic" binding site on the basis of high affinity displacement by several chemically disparate neuroprotective agents. In liver, the [^{3}H]-emopamil binding site is localised to the endoplasmic reticulum.

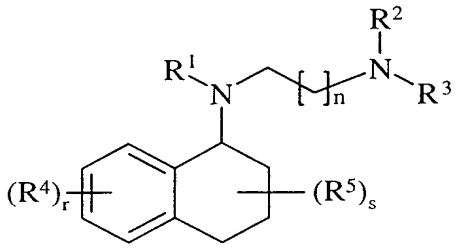
Neuroprotective compounds are known, for example emopamil and ifenprodil, that exhibit high affinity for the [^{3}H]-emopamil binding site. However these are not selective inhibitors and exhibit activity either at neuronal VSCC, the polyamine site of the NMDA receptor (*N*-Methyl-D-aspartate) and/or the sigma-1 binding site. It is thought that compounds that interact with either the VSCC or the NMDA receptor, are responsible for the side effects

usually seen with emopamil, such as hypotension, or those seen with ifenprodil, such as behavioural manifestations.

Summary of The Invention

We have now found a class of compounds that selectively bind at the [^{3}H]-emopamil binding site.

The present invention provides compounds of formula I:



I

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and phenylC_{2-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, phenylsulphonyl, 1-(1,2,3,4-tetrahydronaphthyl), a group of the formula IA:

$$—(CH_2)_p—A$$

IA

wherein A is halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N*,*N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl or *N*,*N*-(C_{1-6}alkyl)$_2$carbamoyl, and p is an integer selected from the range 2 to 6, and a group of the formula IB:

$$—(CR^6R^7)_q—B$$

IB

wherein R^6 and R^7 are independently selected from hydrogen and C_{1-3}alkyl, and B is aryl, a carbon linked heteroaryl, a carbon-linked heterocyclyl, C_{3-12}cycloalkyl or C_{3-12}cycloalkyl fused to a benzene ring; q is an integer selected from the range 0 to 6; and wherein said aryl, heteroaryl or heterocyclyl may be optionally substituted on a ring carbon with one or more M groups where M at each occurrence is independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-

(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylSO_a where a is an integer selected from 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocyclyl or a heteroaryl ring having an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl, or

R^2 and R^3 together with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl ring, where said heterocyclyl or heteroaryl ring may have an -NH- group that may be substituted on the nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl or C_{1-6}alkylsulphonyl, said heterocyclyl or heteroaryl ring may have an -O- group, said heterocyclyl or heteroaryl ring may be optionally substituted with an ortho-fused aryl moiety, and wherein any aforesaid heterocyclyl, heteroaryl ring or aryl moiety may be optionally substituted on a ring carbon with one or more R^9 groups selected from M as heretofore defined,

r is 4 and R^4 at each occurrence is independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, cyano, nitro and C_{2-6}alkenyl;

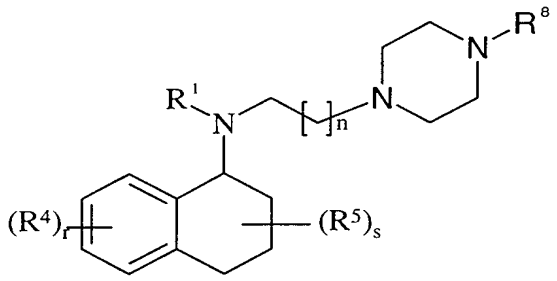
s is 7 and R^5 at each occurrence is independently selected from hydrogen and C_{1-6}alkyl, and

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof;

provided that said compound of formula I is not N,*N*-diethyl-*N'*-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,2-ethanediamine, *N*-propyl-*N'*-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)-1,2-ethanediamine, *N*-propyl-*N'*-(1,2,3,4-tetrahydro-7-methoxy-1-naphthalenyl)-1,2-ethanediamine, *N*-propyl-*N'*-(1,2,3,4-tetrahydro-8-methoxy-1-naphthalenyl)-1,2-ethanediamine or *N*-propyl-*N'*-(1,2,3,4-tetrahydro-5,8-dimethoxy-1-naphthalenyl)-1,2-ethanediamine.

Particular compounds according to formula I provided by the present invention are compounds having the formula XVII:



XVII

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and phenylC_{2-6}alkyl;

R^8 is selected from hydrogen and C_{1-6}alkyl;

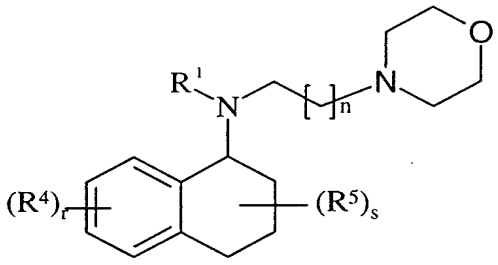
r is 4 and R^4 at each occurrence is independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, cyano, nitro and C_{2-6}alkenyl;

s is 7 and R^5 at each occurrence is independently selected from hydrogen and C_{1-6}alkyl, and

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

Other particular compounds according to formula I provided by the present invention are compounds having the formula XVIII:



XVIII

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and phenylC_{2-6}alkyl, and

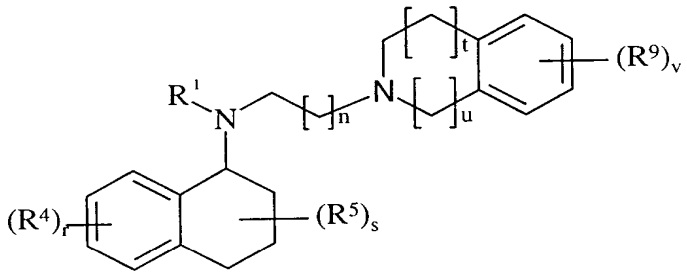
r is 4 and R^4 at each occurrence is independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, cyano, nitro and C_{2-6}alkenyl;

s is 7 and R^5 at each occurrence is independently selected from hydrogen and C_{1-6}alkyl, and

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

Still other particular compounds according to formula I provided by the present invention are compounds having the formula XIX:



XIX

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and phenylC_{2-6}alkyl, and

v is 4 and R^9 is independently selected at each occurrence from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylSO_a where a is an integer selected from 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl;

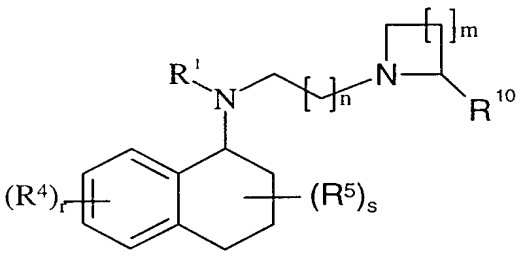
r is 4 and R^4 at each occurrence is independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, cyano, nitro and C_{2-6}alkenyl;

s is 7 and R^5 at each occurrence is independently selected from hydrogen and C_{1-6}alkyl, and

n is 1 or 2, t is 0, 1 or 2, and u is 0 or 1;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

Yet other particular compounds according to formula I provided by the present invention are compounds having the formula XX:



XX

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and phenylC_{2-6}alkyl;

r is 4 and R^4 at each occurrence is independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, cyano, nitro and C_{2-6}alkenyl;

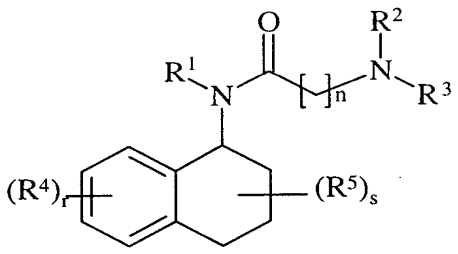
s is 7 and R^5 at each occurrence is independently selected from hydrogen and C_{1-6}alkyl, m is an integer selected from the range 1 to 5;

R^{10} is selected from hydrogen and C_{1-6}alkyl, and

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

Intermediates of compounds according to formula I are provided by the present invention. Such compounds have the formula XXIX:



XXIX

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and phenylC_{2-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, phenylsulphonyl, 1-(1,2,3,4-tetrahydronaphthyl),

a group of the formula IA:

$$—(CH_2)_p—A$$

IA

where A is halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl or *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, and p is an integer selected from the range 2 to 6, and

a group of the formula IB:

$$-(CR^6R^7)_q-B$$

IB

where R^6 and R^7 are independently selected from hydrogen and C_{1-3}alkyl, and

B is aryl, a carbon linked heteroaryl, a carbon-linked heterocyclyl, C_{3-12}cycloalkyl or C_{3-12}cycloalkyl fused to a benzene ring; q is an integer selected from the range 0 to 6; and wherein said aryl, heteroaryl or heterocyclyl may be optionally substituted on a ring carbon with one or more M groups where M at each occurrence is independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylSO_a where a is an integer selected from 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocyclyl or a heteroaryl ring having an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl, or

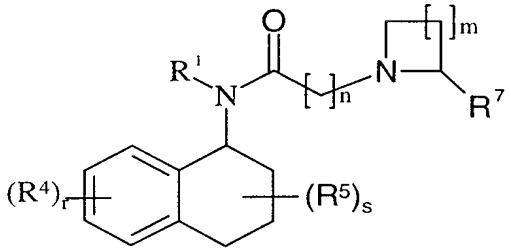
R^2 and R^3 together with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl ring, wherein said heterocyclyl or heteroaryl ring may be optionally substituted on a ring carbon with one or more groups selected from M as heretofore defined, said heterocyclyl or a heteroaryl ring may have an -NH- group that may be substituted on the nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, or said heterocyclyl or a heteroaryl ring may be optionally substituted with an ortho-fused aryl moiety;

r is 4 and R^4 at each occurrence is independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, cyano, nitro and C_{2-6}alkenyl;

s is 7 and R^5 at each occurrence is independently selected from hydrogen and C_{1-6}alkyl, and

n is 1 or 2.

Other intermediates of compounds according to formula I provided by the present invention have the formula XXI:



XXI

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and phenylC_{2-6}alkyl;

r is 4 and R^4 at each occurrence is independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, cyano, nitro and C_{2-6}alkenyl;

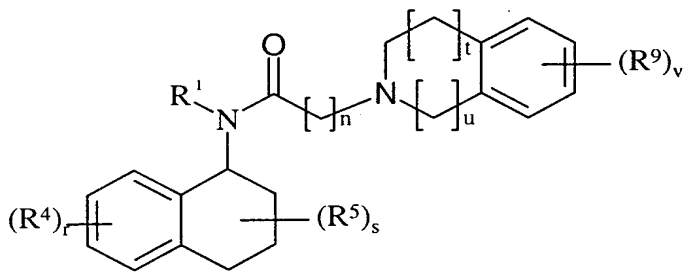
s is 7 and R^5 at each occurrence is independently selected from hydrogen and C_{1-6}alkyl, m is an integer selected from the range 1 to 5;

R^7 is selected from hydrogen and C_{1-6}alkyl, and

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

Further intermediates of compounds according to formula I provided by the present invention have the formula XXII:



XXII

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and phenylC_{2-6}alkyl;

v is 4 and R^9 is independently selected at each occurrence from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylSO_a where a is an integer selected from 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl;

r is 4 and R^4 at each occurrence is independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, cyano, nitro and C_{2-6}alkenyl;

s is 7 and R^5 at each occurrence is independently selected from hydrogen and C_{1-6}alkyl, n is 1 or 2, t is 0, 1 or 2, and u is 0 or 1;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

Detailed description of The Invention

As used herein the term "alkyl," as in for example C_{1-6}alkyl, includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. A similar convention applies to "alkenyl", "alkynyl" and other radicals, for example "phenylC_{1-6}alkyl" includes 2-phenylethyl, 2-phenylpropyl and 3-phenylpropyl.

As used herein "halo" means fluoro, chloro, bromo and iodo.

As used herein, aryl means an unsaturated carbon ring. Particularly aryl is phenyl, naphthyl or biphenyl. More particularly aryl is phenyl.

As used herein, "heteroaryl" or "heteroaryl ring" means, unless otherwise further specified, monocyclic-, bicyclic- or tricyclic- 5-14 membered rings that are unsaturated or partially unsaturated, with up to five ring heteroatoms selected from nitrogen, oxygen and sulphur wherein a -CH_2- group can optionally be replaced by a -C(O)-, and a ring nitrogen atom may be optionally oxidised to form the *N*-oxide. Examples of such heteroaryls include thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, pyridyl, pyridyl-*N*-oxide, oxopyridyl, oxoquinolyl, pyrimidinyl, pyrazinyl, oxopyrazinyl, pyridazinyl, indolinyl, benzofuranyl, benzimidazolyl, benzothiazolyl, quinolyl, isoquinolinyl, quinazolinyl, xanthenyl, quinoxalinyl, indazolyl, benzofuranyl and cinnolinolyl.

As used herein "heterocyclyl" or "heterocyclyl ring" means, unless otherwise further specified, a mono- or bicyclic- 5-14 membered ring, that is totally saturated, with up to five ring heteroatoms selected from nitrogen, oxygen and sulphur wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. Examples of such heterocyclyls include morpholinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, homopiperidinyl, homopiperazinyl and quinuclidinyl.

As used herein, where optional substituents are selected from "one or more" groups it is to be understood that this encompasses compounds where all substituents are chosen from one of the specified groups and compounds where substituents are chosen from more than one of the specified groups.

As used herein terms such as "0 to 6" means each integral value in the stated range, that is, for 0 to 6 the values 0, 1, 2, 3, 4, 5 and 6, similarly, terms such as "range 0 to 2" means the values 0, 1 and 2.

In the present invention, examples of C_{1-6}alkyl include C_{1-4}alkyl moieties such as methyl, ethyl, isopropyl and *t*-butyl; examples of phenylC_{1-6}alkyl include phenylC_{1-4}alkyl moieties such as benzyl, examples of phenylC_{2-6}alkyl include phenylC_{2-4}alkyl moieties such as phenylethyl and phenylpropyl; examples of C_{1-6}alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl; examples of C_{1-6}alkoxy include methoxy, ethoxy and propoxy; examples of C_{1-6}alkanoylamino include formamido, acetamido and propionylamino; examples of C_{1-6}alkylSO_a where a is 0, 1 or 2 include C_{1-6}alkylsulphonyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl; examples of C_{1-6}alkylsulphonyl include mesyl and ethylsulphonyl; examples of C_{1-6}alkanoyl include propionyl and acetyl; examples of *N*-C_{1-6}alkylamino include *N*-methylamino and *N*-ethylamino; examples of *N*,*N*-(C_{1-6}alkyl)$_2$amino include *N*,*N*-dimethylamino, *N*,*N*-diethylamino and *N*-ethyl-*N*-methylamino; examples of C_{3-12}cycloalkyl include cyclopropyl and cyclohexyl; examples of C_{3-12}cycloalkyl fused to a benzene ring are 1,2,3,4-tetrahydronaphthyl and 2,3-dihydroindenyl; examples of C_{2-6}alkenyl include vinyl, allyl and 1-propenyl; examples of C_{2-6}alkynyl include ethynyl, 1-propynyl and 2-propynyl; examples of haloC_{2-6}alkyl include 2-chloroethyl and 2-bromopropyl; examples of *N*-(C_{1-6}alkyl)sulphamoyl include *N*-methylsulphamoyl and *N*-ethylsulphamoyl; examples of *N*,*N*-(C_{1-6}alkyl)$_2$sulphamoyl include *N*,*N*-dimethylsulphamoyl and *N*-methyl-*N*-ethylsulphamoyl; examples of *N*-(C_{1-6}alkyl)carbamoyl include *N*-methylcarbamoyl and *N*-ethylcarbamoyl;

examples of *N*,*N*-(C_{1-6}alkyl)$_2$carbamoyl include *N*,*N*-dimethylcarbamoyl and *N*-methyl-*N*-ethylcarbamoyl; examples of C_{1-6}alkanoyloxy include propionyloxy, acetyloxy and formyloxy. In a particular compound of the invention, R^1 is hydrogen, C_{1-6}alkyl or phenylC_{2-6}alkyl. More particularly R^1 is hydrogen, C_{1-4}alkyl or phenylC_{2-4}alkyl.

Particularly R^1 is hydrogen, methyl or ethyl.

More particularly R^1 is hydrogen or methyl.

In a particularly preferred aspect R^1 is methyl.

In one aspect of the invention, R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl or a group of the formulae IA or IB:

IA IB

as heretofore defined.

In another particular aspect of the invention, R^2 and R^3 together with the nitrogen atom to which they are attached form a ring selected from 1,2,3,4-tetrahydroisoquinolinyl, morpholinyl, piperidinyl, pyrrolidinyl, homopiperidinyl and wherein said ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N*,*N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N*,*N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylSO_a wherein a is an integer selected from the range 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N*,*N*-(C_{1-6}alkyl)$_2$sulphamoyl or phenylC_{1-6}alkyl.

In a further aspect of the invention, R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, or a group of the formula (IB) as depicted above wherein B is aryl, a carbon-linked heterocyclyl, where a heterocyclyl containing an -NH- group may be optionally substituted on the nitrogen with phenylC_{1-6}alkyl, or C_{3-12}cycloalkyl fused to a benzene ring.

In another aspect of the invention, R^2 and R^3 together with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl ring wherein said heterocyclyl ring may be optionally substituted on a ring carbon with one or more groups selected from C_{1-6}alkyl and a heterocyclyl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl.

In another aspect of the invention, R^2 and R^3 are independently selected from methyl, ethyl, isopropyl, phenyl, benzyl or phenylethyl, or R^2 and R^3 together with the nitrogen atom

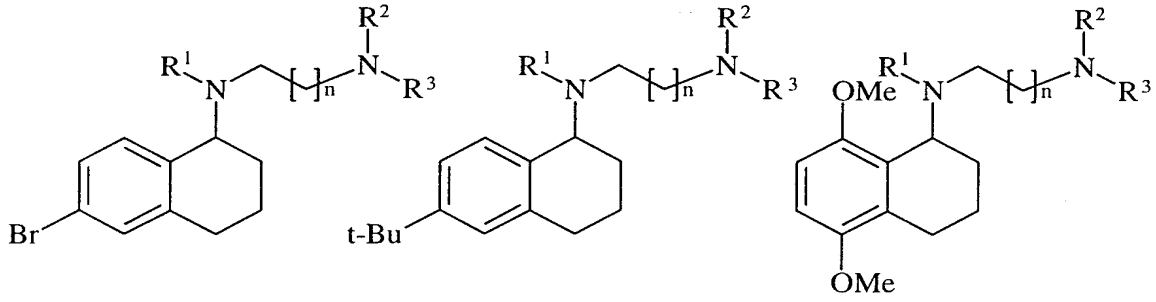
to which they are attached form a pyrrolidin-1-yl, 2-methylpiperidin-1-yl, piperidin-1-yl, 4-methylpiperazin-1-yl, homopiperidin-1-yl or 1,2,3,4-tetrahydroisoquinol-2-yl ring.

In a particular aspect of the invention, R^2 and R^3 are independently selected from methyl, ethyl, isopropyl, benzyl or phenylethyl, or R^2 and R^3 together with the nitrogen atom to which they are attached form a 2-methylpiperidin-1-yl, piperidin-1-yl, homopiperidin-1-yl or 1,2,3,4-tetrahydroisoquinol-2-yl ring.

More particularly R^2 and R^3 are ethyl or R^2 and R^3 together with the nitrogen to which they are attached form a piperidin-1-yl or 1,2,3,4-tetrahydroisoquinol-2-yl ring.

In particular aspects of the invention, R^4 at each occurrence is selected from hydrogen, hydroxyC_{1-6}alkyl, C_{2-6}alkenyl, halo or C_{1-6}alkyl. More particularly R^4 at each occurrence is selected from hydrogen, halo or C_{1-4}alkyl. Particularly R^4 at each occurrence is selected from hydrogen, bromo, 2-hydroxy-2-propyl, 2-propenyl, *tert*-butyl or methyl.

Still more particularly compounds of the invention are selected from compounds of formulae XXX, XXXI and XXXII,



XXX XXXI XXXII

wherein R^1, R^2, R^3 and n are as defined heretofore for compounds of formula I.

In a particular aspect of the invention, R^5 moieties are selected from hydrogen and C_{1-4}alkyl. More particularly R^5 moieties are selected from hydrogen, methyl and ethyl. Most particularly R^5 moieties are selected from hydrogen and methyl. Particularly all R^5 moieties are hydrogen.

In particular aspects of the invention n is an integer selected from 1 or 2.

Therefore, in a particular aspect of the invention there is provided a compound of formula I as depicted above wherein:

R^1 is hydrogen, C_{1-6}alkyl or phenylC_{2-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, or R^2 or R^3 is a group of the formula IB as described herein wherein B is phenyl, a carbon-linked heterocyclyl,

where a heterocyclyl containing an -NH- group may be optionally substituted on this nitrogen with phenylC_{1-6}alkyl, or C_{3-12}cycloalkyl fused to a benzene ring and q is an integer selected from the range 0 to 6, or

R^2 and R^3 together with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl ring, wherein said heterocyclyl or heteroaryl ring optionally contains one further heteroatom selected from oxygen or nitrogen and wherein said heterocyclyl ring may be optionally substituted on a ring carbon with one or more groups selected from C_{1-6}alkyl and a heterocyclyl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl;

R^4 is hydrogen, halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl or C_{2-6}alkenyl where each R^4 may be the same or different and at least one R^4 moiety is hydrogen;

R^5 is hydrogen or C_{1-4}alkyl where each R^5 may be the same or different and at least one R^5 moiety is hydrogen;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

In a more particular aspect of the invention there is provided a compound of the formula I as depicted above wherein:

R^1 is hydrogen, C_{1-4}alkyl or phenylC_{2-4}alkyl;

R^2 and R^3 are independently selected from methyl, ethyl, isopropyl, phenyl, benzyl or phenylethyl, or

R^2 and R^3 together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, 2-methylpiperidin-1-yl, piperidin-1-yl, 4-methylpiperazin-1-yl, homopiperidin-1-yl or 1,2,3,4-tetrahydroisoquinol-2-yl ring;

R^4 is hydrogen, halo or C_{1-4}alkyl where each R^4 may be the same or different and at least two R^4 moieties are hydrogen;

R^5 is hydrogen, methyl or ethyl where each R^5 may be the same or different and at least two R^5 moieties are hydrogen, and

n is 1,

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

In a particular aspect of the invention there is provided a compound of formula I as depicted above wherein:

R^1 is hydrogen, methyl or ethyl;

one of R^2 and R^3 is methyl and the other is phenyl, benzyl or phenylethyl, or

one of R^2 and R^3 is hydrogen and the other is isopropyl, benzyl, 1,2,3,4-tetrahydronapth-1-yl or *N*-(phenylethyl)piperidin-4-yl, or

R^2 and R^3 are the same group and are selected from methyl, ethyl and isopropyl, or

R^2 and R^3 together with the nitrogen atom to which they are attached form a pyrrolidin1-yl, 2-methylpiperidin-1-yl, piperidin-1-yl, 4-methylpiperazin-1-yl, morpholino, homopiperidin-1-yl or 1,2,3,4-tetrahydroisoquinol-2-yl ring;

one R^4 moiety is bromo, or two R^4 moieties are methyl and other R^4 moieties are hydrogen; and

R^5 is always hydrogen, and

n is 1,

or a pharmaceutically-acceptable salt or and *in vivo*-hydrolysable ester, amide or carbamate thereof.

In a still more particular aspect of the invention there is provided a compound of formula I as depicted above wherein:

R^1 is hydrogen or methyl;

one of R^2 and R^3 is methyl and the other is benzyl or phenylethyl, or

R^2 and R^3 are the same group and are selected from ethyl or isopropyl, or

R^2 and R^3 together with the nitrogen atom to which they are attached form a 2-methylpiperidin-1-yl, piperidin-1-yl, homopiperidin-1-yl, pyrrolidin-1-yl or a 1,2,3,4-tetrahydroisoquinol-2-yl ring;

the R^4 is always hydrogen, or R^4 at the 6- position is bromo, or R^4 at the 5 and 8 positions is methyl; and

R^5 is hydrogen, and

n is 1,

or a pharmaceutically-acceptable salt or and *in vivo*-hydrolysable ester, amide or carbamate thereof.

In a yet more particular aspect of the invention there is provided a compound of formula I as depicted above wherein:

R^1 is methyl;

R^2 and R^3 are both ethyl, or

R^2 and R^3 together with the nitrogen to which they are attached form a piperidin-1-yl or 1,2,3,4-tetrahydroisoquinol-2-yl ring;

the R^4 is always hydrogen, or R^4 at the 6- position is bromo, or R^4 at the 5 and 8 positions is methyl; and

R^5 is hydrogen, and

n is 1

or a pharmaceutically-acceptable salt or and *in vivo*-hydrolysable ester, amide or carbamate thereof.

Particular compounds of the invention are those of the examples herein.

Suitable pharmaceutically-acceptable salts include acid-addition salts such as methanesulphonate, fumarate, hydrochloride, hydrobromide, citrate, maleate, phosphate and sulphate. In another aspect suitable salts are base salts such as an alkali metal salt, for example sodium, an alkaline earth metal salt, for example calcium or magnesium, an organic amine salt, for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine and *N,N*-dibenzylethylamine, or amino acids, for example lysine. A compound of the invention may have more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is a sodium salt.

Compounds of formula I possess a chiral centre at the 1-position of the 1,2,3,4-tetrahydronaphthalene ring. Certain compounds of formula I may also have other chiral centres, for example certain of the values of R^1, R^2, R^3, R^4, R^5 and certain of the optional substituents may possess chiral centres. It is to be understood that the invention encompasses all such optical isomers and diastereoisomers of compounds of formula I that act at the [^{3}H]-emopamil binding site.

The invention further relates to all tautomeric forms of the compounds of formula I.

It is also to be understood that certain compounds of the formula I can exist in unsolvated as well as solvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated and unsolvated forms.

As used herein, *in vivo*-hydrolysable esters, amides and carbamates are compounds that hydrolyse in the human body to produce the parent compound. Such esters, amides and carbamates can be identified by administering, for example intravenously to a test animal, the

compound under test and subsequently examining the test animal's body fluids. Suitable *in vivo*-hydrolysable amides and carbamates include *N*-carbomethoxy and *N*-acetyl.

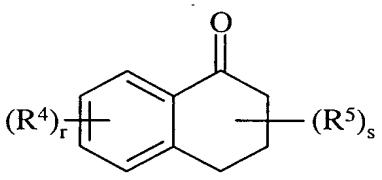
An *in vivo*-hydrolysable ester of a compound of the formula I containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically-acceptable esters for carboxy include C_{1-6}alkoxymethyl esters, for example methoxymethyl; C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl; phthalidyl esters; C_{3-8}cycloalkoxy-carbonyloxyC_{1-6}alkyl esters, for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters, for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group of a compound of the present invention.

An *in vivo*-hydrolysable ester of a compound of the formula I containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester yield the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo*-hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

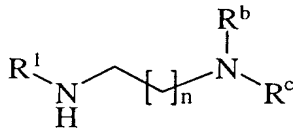
Another aspect of the present invention provides a process for preparing compounds of formula I wherein R^1, R^2, R^3, R^4, R^5 and n, are, unless otherwise specified, as defined in formula I which process comprises:

a) reacting a ketone of formula II:



II

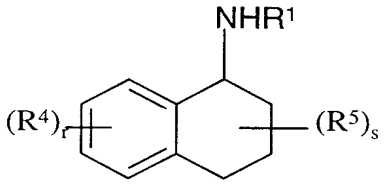
with an amine of formula III:



III;

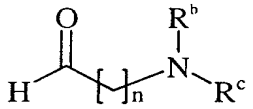
wherein: when R^2 or R^3 of a compound of formula I is hydrogen R^b and R^c are suitable amino protecting groups such as those defined below; or when R^2 or R^3 of a compound of formula I is not hydrogen R^b and R^c are R^2 and R^3 respectively; or

b) reacting an amine of formula IV:



IV

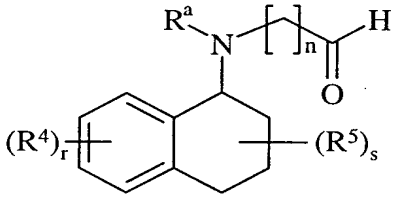
with an aldehyde of formula V:



V

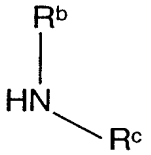
wherein R^b and R^c are as defined above; or

c) reacting an aldehyde of formula VI:



VI

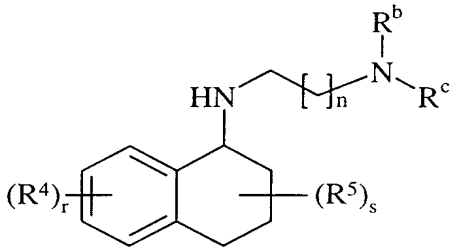
with an amine of formula:



VII

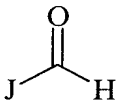
wherein: when R^1 of a compound of formula I is hydrogen R^a is suitable amino protecting group such as those defined below; or when R^1 of a compound of formula I is not hydrogen R^a is R^1; or

d) if R^1 is C_{1-6}alkyl or phenylC_{2-6}alkyl, reacting a compound of formula VIII:



VIII

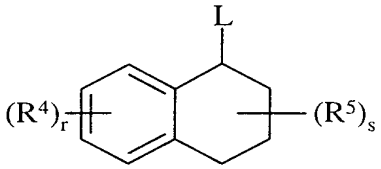
wherein R^b and R^c are as defined above, with a compound of formula IX;



IX

wherein J is hydrogen, C_{1-5}alkyl, or phenylC_{1-5}alkyl; or

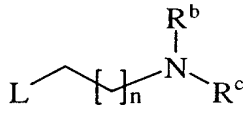
e) reacting a compound of formula X:



X

wherein L is a suitable displaceable group, with an amine of formula III; or

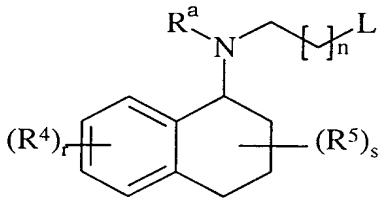
f) reacting an amine of formula IV with a compound of formula XI:



XI

wherein L is a suitable displaceable group and R^b and R^c are as defined above; or

g) reacting a compound of formula XII:



XII

wherein L is a suitable displaceable group, with an amine of formula VII; or

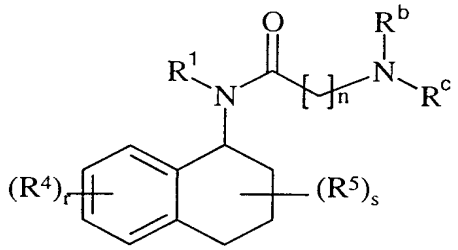
h) if R^1 is not hydrogen, reacting a compound of formula VIII with a compound of formula XIII:

R^1-L

XIII

wherein L is a suitable displaceable group; or

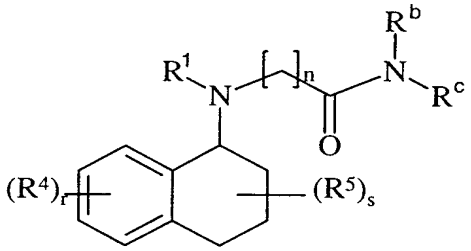
i) reducing a compound of formula XIV:



XIV

or

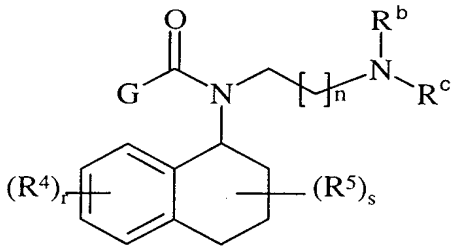
j) reducing a compound of formula XV:



XV

or

k) reducing a compound of formula XVI:



XVI

wherein:

for e), f), g) and h) suitable values for L are a halogeno or sulphonyloxy group, for example: chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy;

for k), suitable values for G are C_{1-6}alkoxy, for example methoxy or ethoxy;

and thereafter if necessary:

i) converting a compound of the formula I into another compound of the formula I;

ii) removing any protecting groups; or

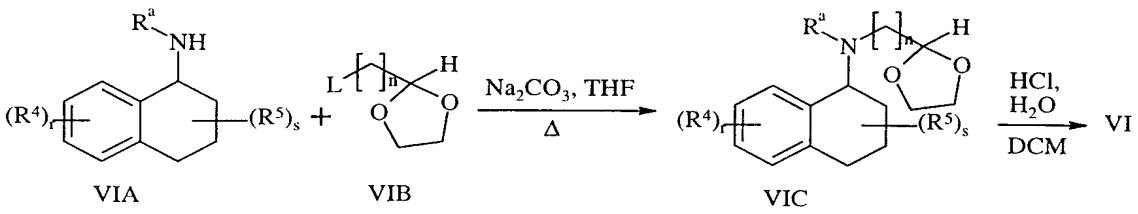
iii) forming a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or carbamate.

Specific reaction conditions for reactions a), b), c) and d) are as follows:

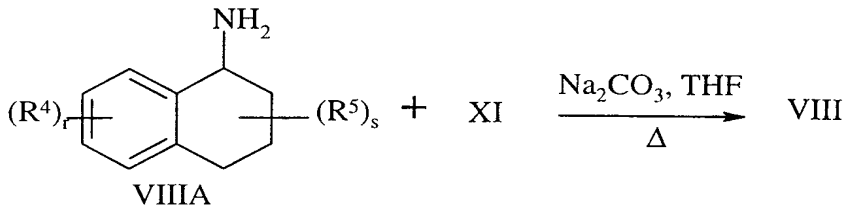
Ketones or aldehydes may be reacted with amines under standard reductive amination conditions. For example in the presence of a reducing agent such as hydrogen and a hydrogenation catalyst (for example palladium on carbon), or zinc and hydrochloric acid, or sodium cyanoborohydride, or sodium triacetoxyborohydride, or sodium borohydride, iron pentacarbonyl and alcoholic potassium hydroxide, or borane and pyridine or formic acid. The reaction is preferably carried out in the presence of a suitable solvent such as an alcohol, for example methanol or ethanol, and at a temperature in the range of 0-50 °C, preferably at or near room temperature.

Compounds of formula II, III, IV, V, VII and IX are commercially available compounds, or are described in the literature, or are prepared by standard processes known in the art.

Compounds of formula VI may be prepared according to the following scheme:



Compounds of formula VIII may be prepared according to the following scheme:



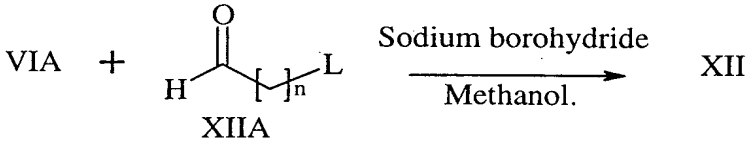
Compounds of formula VIA, VIB and VIIIA are commercially available compounds, or are described in the literature, or are prepared by standard processes known in the art.

Specific reaction conditions for reactions e), f), g) and h) are as follows:

Amines and compounds with suitable leaving groups are reacted together under standard alkylation conditions. For example in the presence of a base, such as an inorganic base for example sodium carbonate or sodium hydroxide, in the presence of an inert solvent for example tetrahydrofuran or toluene and at a temperature in the range of 50-120 °C, preferably at or near reflux.

Compounds of formula X, XI and XIII are commercially available compounds, or are described in the literature, or are prepared by standard processes known in the art.

Compounds of formula XII may be prepared according to the following scheme.

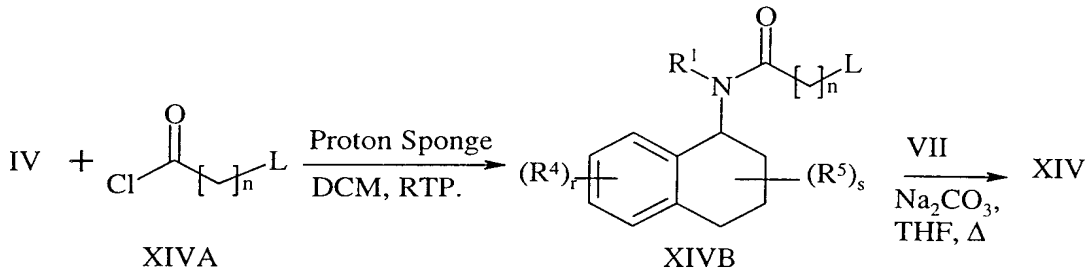


Compounds of formula XIIA are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Specific reaction conditions for reactions i), j) and k) are as follows:

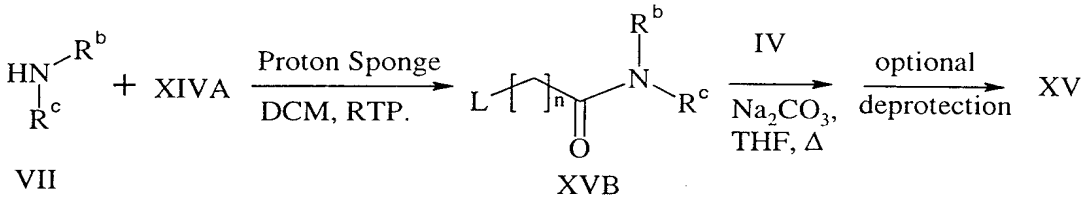
Compounds of formula XIV, XV and XVI are reduced under standard reduction conditions for reducing an amide to an amine. For example, in the presence of a reducing agent such as borane, sodium borohydride or lithium aluminium hydride, in an inert solvent such as toluene or tetrahydrofuran, and at a temperature in the range of 50-120 °C, preferably at or near reflux.

Compounds of formula XIV may be prepared according to the following scheme:



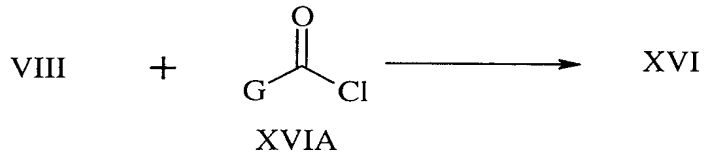
Certain compounds of formula XIV wherein R^1 is not hydrogen bind selectively at the [^{3}H]-emopamil binding site as described in the examples herein.

Compounds of formula XV may be prepared according to the following scheme:



wherein R^b, R^c and L are as hereinbefore defined.

Compounds of formula XVI may be prepared according to the following scheme:



Compounds of formula XIVA and XVIA are commercially available compounds, or are described in the literature, or are prepared by standard processes known in the art.

When an optically active form of a compound of the formula I is required, it may be obtained, for example, by carrying out one of the aforesaid procedures using an optically active starting material or by resolution of a racemic form of said compound using a conventional procedure.

An example of converting one compound of formula I into another compound of formula I is the conversion of R^1, R^2 or R^3 when they are hydrogen to a different R^1, R^2, or R^3. For example, an alkyl group could be introduced by standard alkylation or reductive amination techniques, such as those described above.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either before or following the

processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis

acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

In order to use a compound of the formula I or a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or carbamate thereof for the therapeutic treatment or prophylactic treatment of mammals including humans, such a compound would normally be formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The pharmaceutical compositions of compounds of this invention may be administered in standard manner for the disease condition that it is desired to treat such as stroke, head trauma, transient cerebral ischaemic attack, and chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia. Such pharmaceutical compositions may be administered, for example, by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous

or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions. A preferred route of administration is intravenously in sterile isotonic solution.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be simultaneously or sequentially co-administered with, one or more pharmacological agents of value in treating one or more disease conditions as described herein.

Pharmaceutical compositions comprising compounds of this invention will normally be administered to humans so that, for example, a daily dose of 0.05 to 75 mg/kg body weight (and preferably of 0.1 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

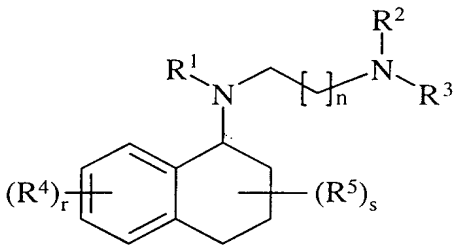
Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula I as defined hereinbefore or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, in association with a pharmaceutically-acceptable excipient or carrier.

According to a further aspect of the present invention there is provided a compound of the formula I or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

A further feature of the present invention is a compound of formula I and pharmaceutically-acceptable salts or an *in vivo*-hydrolysable ester, amide or carbamate thereof, for use as a medicament.

A compound of the present invention suitable for use as a medicament is a compound of formula I:



I

wherein:

R^1 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or phenylC_{2-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, phenylsulphonyl, 1-(1,2,3,4-tetrahydronaphthyl) or a group of the formula IA:

$$—(CH_2)_p—A$$

IA

wherein A is halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl or *N,N*-(C_{1-6}alkyl)$_2$carbamoyl and p is 2 to 6, or

R^2 or R^3 is a group of the formula IB:

$$—(CR^6R^7)_q—B$$

IB

wherein:

R^6 and R^7 are independently selected from hydrogen and C_{1-3}alkyl, and

B is aryl, a carbon linked heteroaryl, a carbon-linked heterocyclyl, C_{3-12}cycloalkyl or C_{3-12}cycloalkyl fused to a benzene ring; q is an integer selected from the range 0 to 6; and wherein said aryl, heteroaryl or heterocyclyl may be optionally substituted on a ring carbon with one or more M groups where M at each occurrence is independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylSO_a wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl; and a heterocyclyl or a heteroaryl ring containing an -NH- group may be

optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl, or

R^2 and R^3 together with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl ring, wherein said heterocyclyl or heteroaryl ring may be optionally substituted on a ring carbon with one or more groups selected from M as heretofore defined, said heterocyclyl or a heteroaryl ring may have an -NH- group that may be substituted on the nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, or said heterocyclyl or a heteroaryl ring may be optionally substituted with an ortho-fused aryl moiety;

R^4 at each occurrence is independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, cyano, nitro and C_{2-6}alkenyl;

R^5 at each occurrence is independently selected from hydrogen and C_{1-6}alkyl;

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

Other compounds of the present invention suitable for use as a medicament are compounds according to formula I having formulae XVII, XVIII, XIX or XX as described herein.

Compounds of formula I are useful in medicaments that inhibit the [^{3}H]-emopamil binding site in a warm-blooded animal such as a human being. Thus, according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, in the manufacture of a medicament for use in the inhibition of the [^{3}H]-emopamil binding site in a warm-blooded animal such as a human being. Thus, according to a still further aspect of the invention there is provided the use of compounds of formulae XVII, XVIII, XIX or XX or pharmaceutically-acceptable salts or *in vivo*-hydrolysable esters, amides or carbamates thereof, in the manufacture of a medicament for use in the inhibition of the [^{3}H]-emopamil binding site in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method of selectively inhibiting of the [^{3}H]-emopamil binding site in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formulae I, XVII, XVIII, XIX or XX or a

pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, as defined hereinbefore.

The following Biological Test Methods, Results and Examples serve to illustrate the present invention.

Biological Test Methods

In summary, the binding affinities (IC_{50}) for 75 representative compounds of the invention to the [^{3}H]-emopamil binding site ranged from 7 nM to 261 nM. In contrast, binding affinities (IC_{50}) for 52 representative compounds of the invention from the aforementioned group of 75 to the ^{3}H-D-888 binding site ranged from 1091 nM to 58,415 nM. The assays were perfomed as follows:

^{3}H-Emopamil binding to guinea pig liver membranes

Binding at the [^{3}H]-emopamil binding site was determined by a modification of the method described by Zech et al. (Zech , C., Staudinger R., Mühlbacher, J. and Glossmann, H. Novel sites for phenylalkylamines: characterisation of a sodium-sensitive drug receptor with (-)-^{3}H-emopamil. *Eur. J. Pharm.*, (1991), *208,* 119-130).

Guinea-pig liver membrane preparation:

Male guinea pigs were sacrificed by CO_2 asphyxiation with dry ice. The livers were quickly excised and weighed and rinsed in membrane preparation buffer containing 10 mM Hepes, 1 mM Tris base-EDTA, 250 mM sucrose, pH 7.4. The livers were then minced, homogenised in 10 times volume with a motor driven Teflon-glass homogeniser with three strokes on ice. The homogenate was centrifuged at 1000 x g in a SS34 rotor for 5 minutes at 4 °C. The supernatant was filtered through 4 layers of gauze and then centrifuged at 8000 x g for 10 minutes at 4 °C. This resulting supernatant was centrifuged at 40,000 x g for 15 minutes at 4 °C. The resulting pellet was resuspended in assay buffer and centrifuged again at 40,000 x g for 15 minutes at 4 °C. This pellet was resuspended in assay buffer (2.5 fold with respect to original wet weight) and homogenised with one stroke with the Teflon-glass homogeniser. Aliquots of 1 mL were stored at -70 °C.

Assay Reaction Mixture:

Assay buffer: 10 mM Tris-HCl, 0.1 mM phenylmethylsulfonyl fluoride (PMSF), 0.2% bovine serum albumin (BSA), pH 7.4 at 4 °C.

Radioligand: 0.96 nM (-)-^{3}H-emopamil (Amersham).

Guinea pig liver membranes: 40mg/mL original wet weight.

Compounds: 1-300 nM.

Total volume: 500 µL.

This mixture was incubated for 60 minutes at 37 °C. The incubation was terminated by filtering with a Brandel Cell Harvester over Whatman GF/C filters that had been soaked for at least 120 minutes in 0.3% polyethylenimine (PEI) and washed three times with 5 mL of wash buffer containing 10 mM Tris-HCl, 10 mM $MgCl_2$, 0.2% BSA, pH 7.4 at 25 °C. Specific binding was defined with 10 µM emopamil.

Results:

Seventy five compounds according to formula I bound to the ^{3}H-emopamil binding site of guinea pig liver membranes with IC_{50}'s in the range from 7 nM to 261 nM. In general, compounds of the present invention bound to the [^{3}H]-emopamil binding site with an IC_{50} below 300nM in this test. The following results were obtained for selected compounds binding to the ^{3}H-Emopamil binding site of guinea pig liver membranes.

Example	IC_{50} (nM)
2	23
6	14
8	21
9	53
10	18
15	109
20	56
46	76
50	8
51	18
52	13
57	13
59	16

^{3}H-D-888 binding to rat brain cortical membranes

^{3}H-D-888 binding was determined by a modification of Reynolds et al. (Reynolds ,

I.J., Snowman, A.M. and Synder, S.H. (-)-[^{3}H] Desmethoxyverapamil labels multiple calcium channel modular receptors in brain and skeletal muscle membranes: differentiation by temperature and dihydropyridines. *J. Pharmacol. Exp. Ther.* (1986) *237: no.3*, 731-738).

Rat brain cortical membrane preparation

Male Sprague-Dawley Rats were sacrificed by decapitation and the brains were quickly excised. The cerebellum and brain stem were removed and discarded; and the rest of the brain was rinsed in 320 mM sucrose. The brain was then homogenised in a 10-fold volume of 320 mM sucrose with a motor driven Teflon-glass homogeniser using 10 strokes on ice. The homogenate was spun at 1000 x g for 10 minutes at 4 °C in a SS-34 rotor. The supernatant was then spun at 29,000 x g for 20 minutes. The resulting pellet was resuspended in membrane buffer (5 mM Hepes, 0.2% BSA, pH 7.4) to a final concentration of 60 mg original wet weight/mL.

Assay Reaction Mixture:

Assay buffer: 50 mM Hepes, 0.2% BSA, pH 7.4

Radioligand: 1ηM ^{3}H-D888 (Amersham)

Rat cortical membranes: 6 mg/mL original wet weight

Compounds: 0.3-100 μM

Total volume: 1000 μL

This mixture was incubated for 60 minutes at 25 °C. The assay was terminated by filtering with a Brandel Cell Harvester over Whatman GF/C filters that had been soaked for at least 120 minutes in 0.3% polyethylenimine (PEI) and washed three times with 5 mL of wash buffer containing 20 mM Hepes, 20 mM $MgCl_2$, pH 7.4. Specific binding was measured with 10 μM methoxyverapamil (D-600). This assay was used to determine *in vitro* selectivity of compounds vs. L-type voltage sensitive calcium channels, i.e. high affinity for the ^{3}H-D888 binding site would show a lack of selectivity.

Results:

Fifty-nine compounds according to formula I bound to the ^{3}H-D-888 binding site of rat brain cortical membranes with IC_{50}'s in the range from 1091 nM to 58,415 nM. In general, compounds of the present invention bound to the ^{3}H-D-888 binding site with an IC_{50} above 3000 nM in this test. The following results were obtained for selected compounds binding to the ^{3}H-D-888 binding site of rat brain cortical membranes.

Example	IC_{50} (nM)
6	7590
8	20813
9	9322
10	10312
46	25951
50	38555
51	1975
52	1117
57	27421
59	33073

Gerbil Global Model of Cerebral Ischaemia

Male Mongolian gerbils (Charles River) weighing 60-70 grams are used in these experiments. They are housed in individual cages with food (Purina Rodent Chow) and water available *ad libitum*. The animal room is maintained at 23 ± 2 °C, and is on an automatic 12 hour light cycle.

The gerbils are brought to the surgical suite and dosed intraperitoneally with the test agent or vehicle, forty-five minutes prior to surgery. Drugs are administered at a volume of 5 mL/kg (intraperitoneal). Vehicle is generally saline, with sodium phosphate added to adjust the pH, if needed. Forty-five minutes after dosing the gerbils are anaesthetised with halothane (3.3%) which is delivered along with oxygen (1.5 l/M) through a face mask. After the gerbils are anaesthetised, halothane is continued at a maintenance level of 1.5-2 % along with oxygen. The ventral surface of the neck is shaved and cleaned with alcohol. Surgical procedures are carried out on a thermostat-controlled heating pad set to 37 °C. An incision is made in the neck, the carotid arteries are dissected away from the surrounding tissue, and isolated with a 5 cm length of Silastic tubing. When both arteries have been isolated they are clamped with microaneurysm clips (Roboz Instruments). The arteries are visually inspected to determine that the blood flow has been stopped. After 5 minutes the clips are gently removed from the arteries and blood flow begins again. A sham control group is treated identically but is not subjected to carotid artery occlusion. The incisions are closed with suture and the gerbils

removed from the anaesthesia masks and placed on another heating pad to recover from the anaesthesia. When they have regained the righting reflex and are beginning to walk around, they are again dosed with the test compound and returned to their home cages. This occurs approximately five minutes after the end of surgery.

Twenty-four hours post ischaemia gerbils are tested for spontaneous locomotor activity, using a Photobeam Activity System from San Diego Instruments. They are individually placed in Plexiglas chambers measuring 27.5 cm x 27.5 cm x 15 cm deep. The chambers are surrounded by photocells, and every time a beam is broken one count is recorded. Each gerbil is tested for two hours, and cumulative counts are recorded at 30, 60, 90, and 120 minutes. Mean counts are recorded for each group and drug groups are compared to control with an ANOVA and Bonferroni post test. After each gerbil is tested it is returned to its home cage. At this time gerbils are also observed for any changes from normal behaviour.

Results:

The following results were obtained for selected compounds tested for efficacy in the foregoing assay.

Example	(% protection)
6	69
8	71.08
9	102.32
10	115.56
50	48.03
51	86.8
57	73.61
59	109.79

Transient focal ischaemia in rats

The method was performed substantially as described by Lin et al. (Lin, T-N., He, Y.Y., Wu, G., Khan, M. And Hsu, C.Y. Effect of brain edema on infarct volume in a focal model cerebral ischaemia model in rats. *Stroke,* (1993), *24,* 117-121). This model is generally considered to be relevant to the clinical situation. Male Long-Evans rats 250-350 g were used.

Surgery to establish a focal ischaemia was conducted under anaesthesia induced with 100 mg/kg ketamine and 5 mg/kg i.m. xylazine. Rectal temperature was monitored and maintained at 37.0 ± 0.5 °C. The right middle cerebral artery (MCA) was exposed using microsurgical techniques. The MCA trunk was ligated immediately above the rhinal fissure with 10-0 suture. Complete interruption of blood flow was confirmed under an operating microscope. Both common carotid arteries were then occluded using nontraumatic aneurysm clips. After a predetermined duration of ischaemia (45 min), blood flow was restored in all three arteries. Twenty-four hours post occlusion, rats were killed under ketamine anesthesia by intracardiac perfusion with 200 mL of 0.9% NaCl. The brain was removed and processed with 2% triphenyltetrazolium chloride to identify and quantitate the infarcted brain region. Compounds were administered by intravenous infusion for 4 hours.

Results:

The following results were obtained for selected compounds tested in the foregoing assay.

Example	Activity(mg/kg/hr)(hr)
6	Active (2)(4)
9	Active (10)(4)
10	Active (10)(4)
46	Active (10)(4)
51	Active (4)(4)

Permanent focal ischaemia in rats

Animal preparation

Sprague-Dawley CD (Charles River) rats 250g-300g were used. Anaesthesia was induced with 5% halothane, reducing to 3% then 1.5%, with approximately 30% N_2O and 65% O_2. The left femoral vein was cannulated with cannula filled with 0.4 ml of 100 i.u./ml heparin prior to use and the cannula exteriorised through the tail. A tail cuff was fitted. Test substance or saline was infused (blinded) at 3.3 ml/kg/hr, halothane was reduced to 1%, then after 5-10 min, surgery was performed as described below.

The right carotid surgically exposed and ligated. An incision was made above the left eye and scalp muscle retracted, and a 3mm trochar hole was made above the zygomatic arch. The middle cerebral artery was exposed using bone nibblers and the dura removed. The main

branch of the middle cerebral artery was occluded below the bifurcation by cauterisation using a Surgicare Hi-Temp Fine-Tip device Model 8500. Typically 2-4 branches were also cauterised. The left carotid was then clipped, the time recorded and the muscle and skin were sutured.

The rats were moved to another anaesthetic station. N_2O was withdrawn and animals were maintained on 1% halothane, 40% air, 60% O_2 for 1 hour without monitoring of the pO_2 and pCO_2. The right carotid clip was then removed and the incision sutured. Animals were removed from anaesthesia and allowed to recover. 'Temgesic' 0.012ml (0.03 mg/ml) s.c. was administered under the direction of a veterinary surgeon as soon as the animals became mobile and exhibited normal gait and cage exploration. Animals were then moved to a lit holding room.

Sample preparation

Samples were prepared in saline adjusted to give a clear solution pH 6-6.5

MRI

After 23-25 hours animals were anaesthetised using 3% halothane and maintained at 2% halothane. They were placed in a stereotactic head frame with ear bars and tooth bars and maintained at 38 °C. The stereotactic device was placed within a 63mm birdcage coil in a 4.7 T magnet. ECG was monitored. Following siting scans, tuning and shimming, a multislice T2-weighted MRI data set was acquired using a Varian INOVA console using the following parameters: Non-fat-suppressed spin-echo; TE= 60msec; TR= 2100 msec; slice thickness= 1 mm; Field of view= 50x50mm; Matrix 256x256.

Segmentation

Segmentation was performed using the region-growing algorithms within 'Tosca' v2.5 (IBM) segmentation software. The endpoint was volume in voxels. This was converted to volume in ml with the aid of a standard calibration factor.

Statistical analysis

A sequential design was used. The study was powered to have a 5% false positive and 5% false negative probability, assuming the true neuroprotection is at least 40%, in a one-sided homoscedastic t-test in log space, assuming CoV (saline) =40% and CoV (treated) =40%. The critical values in the sequential design were:

Critical N (i.e. at least N treated and at	6	9	12	15

least N untreated)				
P value Active	0.00377	0.0154	0.0312	0.0419
P value Inactive	0.68	0.295	0.1049	0.0419

Results:

The following results were obtained for selected compounds tested in the foregoing assay.

Example	Activity(mg/kg/hr)(hr)
6	Active (2)(4)
50	Active (5)(5)
52	Active (4)(4)
57	Active (5)(4)

Examples

The Examples which follow are intended to illustrate but not limit the invention. In the Examples, unless otherwise stated:-

(i) concentrations were carried out by rotary evaporation *in vacuo*;

(ii) operations were carried out at ambient temperature, that is in the range 18-26 °C and under a nitrogen atmosphere;

(iii) column chromatography (by the flash procedure) was performed on Merck Kieselgel silica (Art. 9385);

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the formula I were generally confirmed by NMR and mass spectral techniques; proton magnetic resonance spectra were determined in DMSO-d_6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz; chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; bs, broad singlet; d, doublet; AB or dd, doublet of doublets; t, triplet; dt, double of triplets; m, multiplet; bm, broad multiplet; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and,

where appropriate, either positive ion data or negative ion data were collected, herein $(M+H)^+$ is quoted;

(vi) intermediates were not generally fully characterised and purity was in general assessed by mass spectral (MS) or NMR analysis; and

(vii) in which the following abbreviations (also used hereinabove) may be used:

DMF	is N,*N*-dimethylformamide
DMSO	is dimethylsulphoxide
$CDCl_3$	is deuterated chloroform
m/s	is mass spectroscopy
THF	is tetrahydrofuran
DCM	is dichloromethane
NMP	is *N*-methylpyrrolidone.

Example 1

N^1,N^1-Diisopropyl-N^2-[1,2,3,4-tetrahydro-1-naphthalenyl]-1,2-ethanediamine.

α-Tetralone (0.837g, $5.72x10^{-3}$ mole) and 2-(diisopropylamino)ethylamine (5.165g, $3.58x10^{-2}$ mole) were combined in toluene (30 mL) and cooled to 0 °C (ice/water/sodium chloride). The mixture was treated with titanium tetrachloride solution (1.0M in toluene, 3.0 mL, $3.0x10^{-3}$ mole), maintaining the reaction temperature at < 5 °C. Upon complete addition, additional toluene (20 mL) was added to improve stirring and the mixture was stirred at ambient temperature for 16 hours. The gel/solid was removed by vacuum filtration and the filtrate was concentrated to a brown residue. A solution of the residue in methanol (30 mL) was treated with sodium borohydride (0.288g, $7.61x10^{-3}$ mole) and the reaction mixture was stirred at ambient temperature for one hour. The solvent was evaporated and the residue partitioned between water and diethyl ether. The aqueous portion was extracted with additional diethyl ether. The combined extracts were washed (water, brine), dried, and evaporated to a brown oil which was purified by chromatography, eluting with 1% NH_4OH: 5% MeOH: 94% CH_2Cl_2 (v/v/v), to give the product as a brown oil (0.810g, 51%). ^1H NMR: 0.85-1.02 (m, 12H), 1.56-2.00 (m, 6H), 2.41-2.80 (m, 5H), 2.88-3.02 (m, 2H), 3.63 (t, 1H), 7.00-7.16 (m, 3H),7.26-7.33 (m, 1H); m/s: 275.

Example 2

N^1,N^1-Diisopropyl-N^2-methyl-N^2-1,2,3,4-tetrahydro-1-naphthalenyl-1,2-ethanediamine.

1-[2-(Diisopropylamino)ethylamino]-1,2,3,4-tetrahydronaphthalene (Example 1) (0.319g, 1.16×10^{-3} mole) was dissolved in methanol (7 mL) and the solution was treated with formaldehyde (37% aqueous, 3.0 mL, 4.00×10^{-2} mole). After one hour, sodium borohydride (0.501g, 1.32×10^{-2} mole) was added in small portions, and the mixture was stirred for 15 hours at ambient temperature. The reaction mixture was evaporated and partitioned between saturated aqueous ammonium chloride and dichloromethane. The aqueous portion was extracted with additional dichloromethane. The combined extracts were washed (brine), dried, and evaporated to a brown oil. Due to the presence of remaining starting material, the product mixture was resubmitted to the reaction conditions described above. The product was purified by chromatography, eluting with 3.0% 2.0 M NH_3 in MeOH: 97% CH_2Cl_2 (v/v), to give the product as a pale yellow oil (0.212g, 63%). ^{1}H NMR: 0.82-0.98 (m, 12H), 1.44-1.68 (m, 2H), 1.84-2.00 (m, 2H), 2.24 (s, 3H), 2.26-2.50 (m, 4H), 2.63-2.76 (m, 2H), 2.80-2.95 (m, 2H), 3.73-3.86 (m, 1H), 6.98-7.17 (m, 3H), 7.56-7.66 (m, 1H); m/s: 289.

Example 3

N^1,N^1-Diethyl-N^2-methyl-N^2-[(1*R*)-1,2,3,4-tetrahydro-1-naphthalenyl]-1,2-ethanediamine.

(*R*)-1-[2-(Diethylamino)ethylamino]-1,2,3,4-tetrahydronaphthalene (Example 34) (3.53g, 1.43×10^{-2} mole) and triethylamine (4.0 mL, 2.87×10^{-2} mole) were combined in tetrahydrofuran (135 mL) and treated with ethyl chloroformate (1.5 mL, 1.57×10^{-2} mole) at ambient temperature. The mixture was stirred for 14.5 hours. The reaction mixture was evaporated and partitioned between water and ether. The aqueous portion was extracted with additional ether. The combined organic portions were washed (aqueous sodium bicarbonate, water, brine), dried, and evaporated to yield a yellow oil (4.52g). A solution of the oil in tetrahydrofuran (100 mL) was treated with lithium aluminium hydride (2.16 g, 5.68×10^{-2} mole) and refluxed for two hours. The reaction mixture was quenched with sodium sulphate decahydrate until effervescence ceased. Additional tetrahydrofuran was added to aid stirring. The reaction mixture was filtered through diatomaceous earth and filtrate evaporated to a yellow oil which was purified by chromatography, eluting with 3% 2.0M NH_3 in MeOH:97%

CH_2Cl_2 (v/v), to give the product as a pale yellow oil (3.54g). NMR: 0.90 (t, 6H), 1.46-1.68 (m, 2H), 1.83-2.00 (m, 2H), 2.19 (s, 3H), 2.31-2.80 (m, 10H), 3.77-3.87 (m, 1H), 7.00-7.17 (m, 3H), 7.56-7.63 (m, 1H); m/s: 261.

Example 4

N-Ethyl-*N*-(3-(4-methylpiperazino)propyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

Borane-methylsulphide complex (1.0 mL, $1.05x10^{-2}$ mole) was added to a solution of 1-[3-(4-methylpiperazin-1-yl)propyl(*N*-acetyl)amino]-1,2,3,4-tetrahydronaphthalene (Example 119) (0.160g, $4.85x10^{-4}$ mole) in tetrahydrofuran (2 mL). The mixture was heated at 70 °C for 18 hours. The reaction mixture was quenched with methanol at ambient temperature and heated at 70 °C for one hour, followed by addition of concentrated hydrochloric acid (1.0 mL) and heating at 70 °C for 10 minutes. The quenched mixture stirred at ambient temperature for 0.5 hour. The solvent was evaporated, and the residue was partitioned between 1M sodium hydroxide and diethyl ether. The aqueous portion was saturated with solid sodium chloride and extracted with additional diethyl ether. The combined extracts were washed (brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1% NH_4OH/5% MeOH: 94% CH_2Cl_2 (v/v/v), to give the product as a pale yellow oil (0.105g, 68%). ^1H NMR: 0.96 (t, 3H), 1.40-1.69 (m, 4H), 1.86-2.03 (m, 2H), 2.12 (s, 3H), 2.13-2.80 (m, 16H), 3.83-3.94 (m, 1H), 6.97-7.16 (m, 3H), 7.61 (d, 1H); m/s: 316.

Example 5

N^1,N^1-Diethyl-N^2-methyl-N^2-[(1*S*)-1,2,3,4-tetrahydro-1-naphthalenyl]-1,2-ethanediamine.

Potassium carbonate (12.9 g, 46.5 mmol) was added to a solution of *(S)*-1-methylamino-1,2,3,4-tetrahydronaphthalene (Smith, R.A.; White, R.L.; Krantz, A., *J. Med. Chem.*, (1988), *31*, 1558-66) (3.0 g, 18.6 mmol) and 2-diethylaminoethyl chloride hydrochloride (8.0 g, 46.5 mmol) in 186 mL of absolute ethanol and the reaction mixture was heated to reflux for 24 hours. The reaction was then cooled and then filtered through a short pad of diatomaceous earth and solvents were removed in vacuo. Purification by silica gel chromatography (15:1 dichloromethane:2M ammonia in methanol) followed by Kugelrohr distillation yielded the titled compound (2.21 g, 45%). NMR ($CDCl_3$): 0.99 (t, 6H), 1.64 (m,

4H), 1.98 (m, 2H), 2.27 (s, 3H), 2.50 (m, 6H), 2.72 (m, 2H), 3.87 (m, 1H), 7.09 (m, 3H), 7.66 (d, 1H); m/s: 261.

Example 6

N-[2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethyl]-*N*-methyl-*N*-[(1*S*)-1,2,3,4-tetrahydronaphthalen-1-yl]amine.

Borane-methylsulphide complex (33.0 mL, 0.348 mole) was added to a solution of (*S*)-1-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)-*N*-methylacetamido]-1,2,3,4-tetrahydronaphthalene (Example 88) (5.87g, 1.76×10^{-2}mole) in THF (80 mL). The mixture was heated at 70 °C for 7.5 hours. The reaction mixture was quenched with methanol (100 mL) and heated at 70 °C for 30 minutes, followed by addition of concentrated HCl (5 mL) and heating for 10 minutes. The quenched mixture stirred at ambient temperature for 12.5 hours. The solvent was evaporated, and the residue partitioned between aqueous 1 M NaOH and ethyl acetate. The aqueous portion was saturated with solid sodium chloride and extracted with additional ethyl acetate. The combined extracts were washed (brine), dried, and evaporated to yield a residue which was purified by chromatography, eluting with 5 % 2.0 M NH_3 in MeOH:95 % CH_2Cl_2 (v/v), to give the product as a pale yellow oil (3.99g). ^{1}H NMR: 1.50-1.67 (m, 2H), 1.87-2.00 (m, 2H), 2.22 (s, 3H), 2.53-2.83 (m, 10H), 3.50-3.59 (m, 2H), 3.81-3.91 (m, 1H), 6.94-7.17 (m, 7H), 7.57-7.65 (m, 1H). m/s: 321.

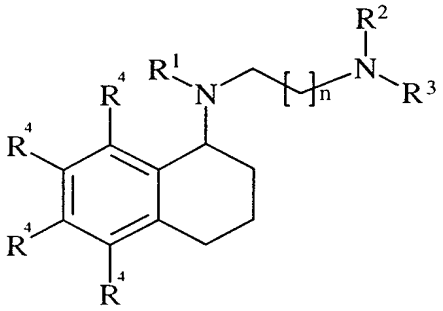
Example 7

1-[2-(*N*-benzyl-*N*-ethyl)ethyl]-(*N*-methyl)-amino-1,2,3,4-tetrahydronaphthalene.

A solution of a compound according to Example 98 (1.02g, 3.03×10^{-3} mole) in THF (25 mL) was treated with lithium aluminum hydride (0.46g, 1.22×10^{-3} mole) and refluxed for 3.5 hours. The reaction mixture was quenched with sodium sulfate decahydrate until effervescence ceased. Additional THF and diethyl ether were added to aid stirring. The reaction mixture was filtered through diatomaceous earth and the filtrate evaporated to a yellow oil which was purified by chromatography, eluting with 3% 2.0 M NH_3 in methanol:97% DCM (v/v), to give the product as a pale yellow oil (0.82 g, 84%). ^{1}H NMR: 0.94 (t, 3H), 1.41-1.66 (m, 2H), 1.81-1.98 (m, 2H), 2.13 (s, 3H), 2.35-2.78 (m, 8H), 3.52 (s, 2H), 3.74-3.84 (m, 1H), 6.97-7.13 (m, 3H), 7.17-7.36 (m, 5H), 7.51-7.60 (m, 1H). m/s: 323.

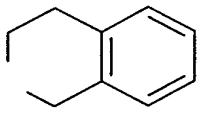
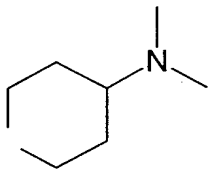
Examples 8-43

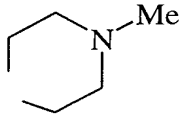
Compounds according to formula XXIII shown in tables 1 and 2 were prepared using procedures analogous to those described in Examples 1-7.

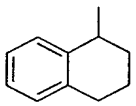


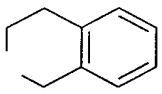
XXIII

Table 1

Ex	R^1	R^2	R^3	$(R^4)_r$	n	M*	NMR	m/s
8^2	Me	$-(CH_2)_5-$		H	1	3	1.23-1.70 (m, 8H), 1.83-2.00 (m, 2H), 2.18 (s, 3H), 2.17-2.80 (m, 10H), 3.75-3.88 (m, 1H), 6.95-7.19 (m, 3H), 7.52-7.66 (m, 1H)	273
9^1	H	Me	$-CH_2Ph$	H	1	6	1.53-2.00 (m, 5H), 2.11 (s, 3H), 2.42-2.53 (m, 2H), 2.60-2.83 (m, 4H), 3.46 (d, 2H), 3.63 (t, 1H), 7.00-7.36 (m, 9H)	295
10^2	Me			H	1	2	1.49-1.68 (m, 2H), 1.83-2.00 (m, 2H), 2.22 (s, 3H), 2.47-2.82 (m, 10H), 3.53 (s, 2H), 3.80-3.93 (m, 1H), 6.93-7.17 (m, 7H), 7.53-7.63 (m, 1H)	321
11^2	H	Me	$-CH_2Ph$	H	1	6	1.53-2.00 (m, 5H), 2.11 (s, 3H), 2.40-2.82 (m, 6H), 3.46 (d, 2H), 3.65 (t, 1H), 7.00-7.37 (m, 9H)	295
12^1	Me			H	1	7	1.21-1.40 (m, 2H), 1.44-1.70 (m, 4H), 1.78-2.02 (m, 5H), 2.13 (s, 6H), 2.18 (s, 3H), 2.27-2.53 (m, 4H), 2.60-2.88 (m, 4H), 3.77-3.87 (m, 1H), 7.00-7.16 (m, 3H), 7.55-7.61 (m, 1H)	316

13	H	-$(CH_2)_4$-	H	1	1	1.56-2.00 (m, 9H), 2.32-2.80 (m, 10H), 3.64 (t, 1H), 6.98-7.40 (m, 4H)	245
14	Me		H	2	2	1.46-1.69 (m, 4H), 1.83-2.00 (m, 2H), 2.12 (s, 6H), 2.16-2.77 (m, 18H), 3.76-3.85 (m, 1H), 6.98-7.16 (m, 3H), 7.56 (d,1H)	302
15	Me	Me Me	H	1	2	$CDCl_3$: 1.66 (m, 2H), 1.99 (m, 2H), 2.26 (s, 6H), 2.43-2.62 (m, 4H), 2.72 (s, 3H), 2.75 (m, 2H), 3.88 (m, 1H), 6.97-7.23 (m, 3H), 7.70 (m, 1H)	233
16	Me	Me Me	H	2	2	$CDCl_3$: 1.67 (m, 4H), 1.97 (m, 2H), 2.21 (s, 3H), 2.30 (s, 6H), 2.50 (m, 4H), 2.72 (m, 2H), 3.88 (m, 1H), 7.03-7.23 (m, 3H), 7.65 (m, 1H),	247
17	Et	-$(CH_2)_5$-	H	1	4	$CDCl_3$: 1.03 (t, 3H), 1.41 (m, 2H), 1.58 (m, 6H), 2.01 (m, 2H), 2.36-2.83 (m, 12H), 3.94 (dd, 1H), 7.09 (m, 3H), 7.74 (d, 1H)	287
18[3]	H	-$(CH_2)_5$-	6-Br	1	1	$CDCl_3$: 1.43 (m, 2H), 1.53 (m, 4H), 1.71 (m, 1H), 1.86 (m, 2H), 1.94 (m, 1H), 2.36 (br s, 4H), 2.45 (m, 2H), 2.70 (m, 4H), 3.71 (t, 1H), 7.22 (m, 3H)	337, 339
19	Me	-$(CH_2)_5$-	6-Br	1	2	$CDCl_3$: 1.42 (m, 2H), 1.53-1.64 (m, 6H), 1.96 (m, 2H), 2.25 (s, 3H), 2.30-2.68 (m, 10H), 3.78 (m, 1H), 7.21 (m, 2H), 7.55 (d, 1H)	351, 353
20	H	-$(CH_2)_5$-	5-Me 8-Me	1	1	$CDCl_3$: 1.41 (m, 2H), 1.51 (m, 4H), 1.75 (m, 1H), 2.08 (m, 3H), 2.16 (s, 3H), 2.32 (m, 2H), 2.36 (s, 3H), 2.42 (m, 5H), 2.72 (m, 2H), 2.86 (m, 1H), 3.75 (m, 1H), 6.94 (m, 2H)	287
21	Me	-$(CH_2)_5$-	5-Me, 8-Me	1	2	$CDCl_3$: 1.39 (m, 2H), 1.49 (m, 4H), 1.63 (m, 2H), 1.90 (m, 1H), 2.04 (m, 1H), 2.19 (s, 6H), 2.27 (m, 6H), 2.38 (s, 3H), 2.57 (m, 4H), 3.92 (m, 1H), 6.91 (m, 2H)	301

22	H	-$(CH_2)_2O(CH_2)_2$-		H	1	1	$CDCl_3$: 1.69-2.04 (m, 4H), 2 43 (m, 4H), 2.52 (m, 2H), 2.77 (m, 4H), 3.70 (t, 4H), 3.77 (t, 1H), 7.13 (m, 3H), 7.31 (m, 1H),	261
23	H	-$(CH_2)_2O(CH_2)_2$-		H	2	1	$CDCl_3$: 1.66-1.94 (m, 6H), 2.43 (m, 6H), 2.77 (m, 4H), 3.70 (m, 4H), 3.75 (t, 3H), 7.13 (m, 3H), 7.34 (m, 1H)	275
24	H		Me	H	2	1	$CDCl_3$: 1.64-1.95 (m, 7H), 2.78 (m, 4H), 2.92 (s, 3H), 3.41 (m, 2H), 3.75 (t, 1H), 6.71 (m, 3H), 7.19 (m, 5H), 7.34 (m, 1H)	295
25	Me		Me	H	2	2	$CDCl_3$: 1.61-1.80 (m, 4H), 1.96 (m, 2H), 2.19 (s, 3H), 2.52 (t, 2H), 2.74 (m, 2H), 2.93 (s, 3H), 3.44 (m, 2H), 3.89 (m, 1H), 6.71 (m, 3H), 7.17 (m, 5H), 7.71 (d, 1H)	309
26	H	H	-CH_2Ph	H	1	6	1.53-2.23 (m, 6H), 2.52-2.80 (m, 6H), 3.61 (t, 1H), 3.68 (s, 2H), 7.00-7.42 (m, 9H)	281
27	Et	nBu	nBu	H	2	4	0.84 (t, 6H), 0.97 (t, 3H), 1.14-1.68 (m, 12H), 1.85-2.02 (m, 2H), 2.06-2.57 (m, 10H), 2.62-2.77 (m, 2H), 3.83-3.93 (m, 1H), 6.98-7.16 (m, 3H), 7.63 (d, 1H)	345
28	Me	nBu	nBu	H	1	2	0.83 (t, 6H), 1.12-1.40 (m, 8H), 1.43-1.67 (m, 2H), 1.85-2.00 (m, 2H), 2.19 (s, 3H), 2.24-2.80 (m, 10H), 3.77-3.87 (m, 1H), 6.98-7.17 (m, 3H), 7.55-7.62 (m, 1H)	317
29	H	H		H	1	6	1.53-2.03 (m, 10H), 2.53-2.83 (m, 8H), 3.56-3.76 (m, 2H), 6.92-7.19 (m, 6H), 7.25-7.42 (m, 2H)	321
30	Me	nBu	nBu	H	2	2	0.84 (t, 6H), 1.17-1.40 (m, 8H), 1.43-1.68 (m, 4H), 1.82-1.98 (m, 2H), 2.10 (s, 3H), 2.23-2.48 (m, 8H), 2.60-2.75 (m, 2H), 3.77-3.84 (m, 1H), 6.98-7.17 (m, 3H), 7.56-7.62 (m, 1H)	331

31	Me	$-(CH_2)_4CH(Me)-$		H	2	2	0.97 (d, 3H), 1.05-1.70 (m, 11H), 1.82-2.82 (m, 13H), 3.77-3.87 (m, 1H), 6.97-7.17 (m, 3H), 7.54-7.62 (m, 1H)	301
32	H	^{i}Pr	H	H	1	1	$CDCl_3$: 1.09 (d, 6H), 1.70-1.98 (m, 6H), 2.72-2.93 (m, 7H), 3.76 (t, 1H), 7.14 (m, 3H), 7.30 (m, 1H)	233
33[2]	H	$-(CH_2)_5-$		H	1	6	1.23-2.00 (m, 11H), 2.20-2.43 (m, 6H), 2.53-2.80 (m, 4H), 3.64 (t, 1H), 6.98-7.20 (m, 3H), 7.26-7.36 (m, 1H)	259
34[2]	H	Et	Et	H	1	6	0.93 (t, 6H), 1.47-2.00 (m, 5H), 2.32-2.80 (m, 10H), 3.65 (t, 1H), 6.97-7.20 (m, 3H), 7.26-7.34 (m, 1H)	247
35[2]	H			H	1	6	1.56-2.00 (m, 5H), 2.53-2.90 (m, 10H), 3.55 (s, 2H), 3.70 (t, 1H), 7.00-7.20 (m, 7H), 7.27-7.36 (m, 1H)	307

[1] S Enantiomer

[2] R Enantiomer

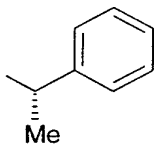
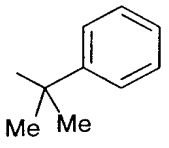
[3] The preparation of 5-bromo-α-tetralone is described in Hanuise, J., Smolders, R.R., *Ing. Chim.*, (1977), *59*, (286), 79-94.

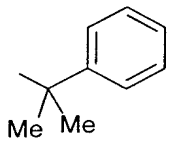
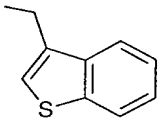
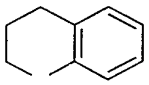
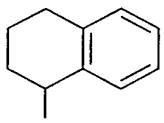
[#] Compound previously described.

M* Made by method of Example Number

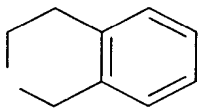
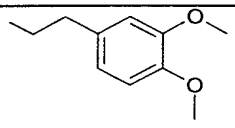
Table 2

Ex	R^1	R^2	R^3	$(R^4)_r$	n	M*	NMR	m/s
36[1]	Me	Me	$-CH_2Ph$	H	1	7	1.47-1.67 (m, 2H), 1.85-2.00 (m, 2H), 2.10 (s, 3H), 2.15 (s, 3H), 2.37-2.89 (m, 6H), 3.45 (s, 2H), 3.76-3.87 (m, 1H), 6.98-7.14 (m, 3H), 7.17-7.38 (m, 5H), 7.54-7.63 (m, 1H)	309
37[1]	Me	$-CH_2CH_2OH$	$-CH_2Ph$	H	1	7	1.43-1.66 (m, 2H), 1.80-1.96 (m, 2H), 2.11 (s, 3H), 2.43-2.80 (m, 8H), 3.37-3.49 (m, 2H), 3.58 (s, 2H), 3.72-3.83 (m, 1H), 4.35 (t, 1H), 7.00-7.12 (m, 3H), 7.13-7.36 (m, 5H), 7.52-7.60 (m, 1H)	339

38[1]	Me	$-(CH_2)_2N(Me)_2$	$-CH_2Ph$	H	1	7	1.43-1.65 (m, 2H), 1.80-1.96 (m, 2H), 2.05 (s, 6H), 2.13 (s, 3H), 2.22-2.33 (m, 2H), 2.40-2.76 (m, 6H), 3.27-3.40 (m, 2H), 3.55 (s, 2H), 3.73-3.84 (m, 1H), 6.97-7.13 (m, 3H), 7.18-7.33 (m, 5H), 7.52-7.60 (m, 1H)	366
39[1]	Me	$-(CH_2)_2CH_3$	$-CH_2Ph$	H	1	7	0.78 (t, 3H), 1.32-1.66 (m, 4H), 1.82-1.97 (m, 2H), 2.12 (s, 3H), 2.32 (t, 2H), 2.40-2.77 (m, 6H), 3.51 (s, 2H), 3.73-3.85 (m, 1H), 6.99-7.12 (m, 3H), 7.16-7.37 (m, 5H), 7.51-7.61 (m, 1H)	337
40[1]	Me	$-(CH_2)_3CH_3$	$-CH_2Ph$	H	1	7	0.79 (t, 3H), 1.13-1.30 (m, 2H), 1.30-1.46 (m, 2H), 1.46-1.67 (m, 2H), 1.80-1.94 (m, 2H), 2.12 (s, 3H), 2.35 (t, 2H), 2.42-2.78 (m, 6H), 3.51 (s, 2H), 3.73-3.84 (m, 1H), 6.97-7.13 (m, 3H), 7.16-7.37 (m, 5H), 7.50-7.58 (m, 1H)	351
41[1]	Me	Me		H	1	7	1.25 (d, 3H), 1.44-1.66 (m, 2H), 1.82-2.00 (m, 2H), 2.08 (s, 3H), 2.11 (s, 3H), 2.24-2.58 (m, 4H), 2.60-2.78 (m, 2H), 3.55 (q, 1H), 3.73-3.82 (m, 1H), 6.98-7.38 (m, 8H), 7.49-7.60 (m, 1H)	323
42[1]	Me	H		H	1	7	1.36 (bs, 6H), 1.47-1.65 (m, 2H), 1.80-1.95 (m, 2H), 2.02 (s, 3H), 2.24-2.79 (m, 7H), 3.70-3.82 (m, 1H), 7.00-7.60 (m, 9H)	323

43[1]	Me	Me		H	1	3	1.25 (d, 6H), 1.40-1.63 (m, 2H), 1.80-1.97 (m, 2H), 2.03 (s, 3H), 2.11 (s, 3H), 2.20-2.44 (m, 4H), 2.60-2.73 (m, 2H), 3.66-3.76 (m, 1H), 6.97-7.10 (m, 3H), 7.13-7.33 (m, 3H), 7.43-7.57 (m, 3H)	337
44[1]	Me	Me		H	1	7	1.44-1.65 (m, 2H), 1.80-2.00 (m, 2H), 2.14 (s, 6H), 2.40-2.80 (m, 6H), 3.70 (s, 2H), 3.76-3.89 (m, 1H), 6.98-7.13 (m, 3H), 7.26-7.40 (m, 2H), 7.51 (s, 1H), 7.53-7.62 (m, 1H), 7.90-8.02 (m, 2H)	365
45	Me			H	1	6	1.40-1.67 (m, 2H), 1.70-2.03 (m, 4H), 2.30 (s, 3H), 2.37-2.80 (m, 6H), 3.13-3.44 (m, 4H), 3.76-3.91 (m, 1H), 6.28-6.46 (m, 2H), 6.73-6.88 (m, 2H), 6.97-7.20 (m, 3H), 7.56-7.67 (m, 1H)	321
46[1]	H	$-(CH_2)_6-$		H	1	7	1.40-2.00 (m, 14H), 2.42-2.80 (m, 8H), 3.33 (bs, 1H), 3.60-3.71 (m, 1H), 7.00-7.20 (m, 3H), 7.26-7.34 (m, 1H)	273
47	Me	$-(CH_2)_6-$		H	1	6	1.45-1.65 (m, 11H), 1.85-2.00 (m, 2H), 2.17 (s, 3H), 2.40-2.80 (m, 9H), 3.78-3.89 (m, 1H), 6.98-7.17 (m, 3H), 7.56-7.62 (m, 1H)	287
48	Me	Me		H	1	6	1.42-1.69 (m, 4H), 1.80-2.01 (m, 4H), 2.08-2.25 (m, 6H), 2.33-2.80 (m, 6.5H), 3.36-3.55 (m, 1H), 3.72-3.89 (m, 2H), 4.30-4.38 (m, 0.5H), 6.96-7.17 (m, 6H), 7.52-7.69 (m, 2H)	349

49[1]	H	-$(CH_2)_5$-		H	1	7	1.23-2.00 (m, 10H), 2.17-2.47 (m, 6H), 2.53-2.80 (m, 4H), 3.33 (bs, 1H), 3.58-3.73 (m, 1H), 6.98-7.20 (m, 3H), 7.23-7.36 (m, 1H)	259
50[1]	Me	-$(CH_2)_5$-		H	1	7	1.28-1.70 (m, 8H), 1.85-1.98 (m, 2H), 2.18 (s, 3H), 2.20-2.78 (m, 10H), 3.77-3.86 (m, 1H), 6.98-7.19 (m, 3H), 7.57-7.63 (m, 1H)	273
51[1]	Me	Me	-$(CH_2)_2$Ph	H	1	7	1.45-1.69 (m, 2H), 1.83-2.00 (m, 2H), 2.17 (s, 3H), 2.20 (s, 3H), 2.36-2.80 (m, 10H), 3.77-3.90 (m, 1H), 7.00-7.30 (m, 8H), 7.55-7.65 (m, 1H)	323
52[2]	Me	Me	-$(CH_2)_2$Ph	H	1	3	1.46-1.69 (m, 2H), 1.83-2.00 (m, 2H), 2.17 (s, 3H), 2.19 (s, 3H), 2.37-2.80 (m, 10H), 3.77-3.87 (m, 1H), 6.98-7.30 (m, 8H), 7.55-7.63 (m, 1H)	323
53[2]	H	Me	-$(CH_2)_2$Ph	H	1	6	1.53-1.93 (m, 5H), 2.21 (s, 3H), 2.42-2.78 (m, 10H), 3.58-3.66 (m, 1H), 7.00-7.30 (m, 9H)	309
54[1]	H	Me	-$(CH_2)_2$Ph	H	1	7	1.53-1.97 (m, 4H), 2.21 (s, 3H), 2.40-2.80 (m, 10H), 3.33 (bs, 1H), 3.60-3.68 (m, 1H), 7.00-7.30 (m, 9H)	309
55[1]	Me	$(CH_2)_5$		H	2	7	$CDCl_3$ 1.43 (m, 2H), 1.62 (m, 8H), 1.96 (m, 2H), 2.19 (s, 3H), 2.38 (m, 8H), 2.75 (m, 2H), 3.87 (m, 1H), 7.02-7.19 (m, 3H), 7.66 (m, 1H)	287

56[2]	Me	$(CH_2)_5$		H	2	7	$CDCl_3$ 1.42 (m, 2H), 1.54-1.75 (m, 8H), 1.95 (m, 2H), 2.19 (s, 3H), 2.31-2.53 (m, 8H), 2.71 (m, 2H), 3.88 (m, 1H), 7.02-7.26 (m, 3H), 7.67 (m, 1H)	287
57[1]	Me	$(CH_2)_4$		H	1	7	$CDCl_3$ 1.63 (m, 2H), 1.75 (m, 4H), 1.99 (m, 2H), 2.28 (s, 3H), 2.48 (m, 4H), 2.66 (m, 4H), 2.72 (m, 2H), 3.89 (m, 1H), 6.98-7.20 (m, 3H), 7.68 (m, 1H)	
58[1]	H			H	1	7	$CDCl_3$ 1.70 (m, 2H), 1.86-2.02 (m, 3H), 2.73 (m, 6H), 2.89 (m, 4H), 3.63 (s, 2H), 3.80 (m, 1H), 7.00-7.14 (m, 7H), 7.30 (m, 1H)	307
59	Me	Et	Et	H	1	2	0.90 (m, 6H), 1.57 (m, 2H), 1.92 (m, 2H), 2.19 (s, 3H), 2.37-2.75 (m, 10H), 3.81 (m, 1H), 7.09 (m, 3H), 7.61 (m, 1H)	261
60	H	$(CH_2)_5$		H	1	1	$CDCl_3$ 1.44 (m, 2H), 1.58 (m, 4H), 1.93 (m, 5H), 2.39 (m, 4H), 2.49 (t, 2H), 2.80 (m, 4H), 3.79 (t, 1H), 7.14 (m, 3H), 7.31 (m, 1H)	259
61[1]	Me	Me		H	1	7	1.47-1.66 (m, 2H), 1.84-1.98 (m, 2H), 2.17 (s, 3H), 2.20 (s, 3H), 2.40-2.80 (m, 10H), 3.69 (s, 3H), 3.70 (s, 3H), 3.77-3.87 (m, 1H), 6.63-6.71 (m, 1H), 6.75-6.86 (m, 2H), 7.00-7.16 (m, 3H), 7.55-7.64 (m, 1H)	383

[1] S Enantiomer
[2] R Enantiomer
M* Made by method of Example Number

Example 62

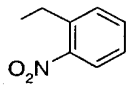
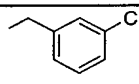
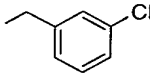
N^1-2-Cyanobenzyl-N^1-methyl-N^2-methyl-N^2-[(1,*S*)-1,2,3,4-tetrahydronaphthalen-1-yl]ethane-1,2-diamine.

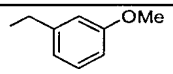
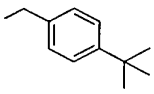
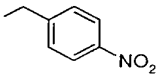
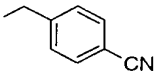
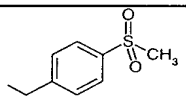
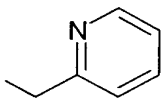
1-[2-(Methylamino)ethylamino]-1,2,3,4-tetrahydronaphthalene (Example 122) (0.704g, 3.22×10^{-3} mole) and potassium carbonate (0.477g, 3.23×10^{-3} mole) were combined in acetonitrile (20 mL) according to the foregoing scheme. 2-Cyanobenzyl bromide (0.629g, 3.21×10^{-3} mole) was added to the mixture and washed in with additional acetonitrile (22 mL). The mixture was refluxed for two hours, then concentrated under reduced pressure. The residue was partitioned between water and DCM. The aqueous portion was extracted with additional DCM. The combined organic portions were washed (water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 3% 2.0M NH_3 in MeOH:97% DCM (v/v), to give the product as a yellow oil (1.02 g, 95%). ^{1}H NMR: 1.45-1.68 (m, 2H), 1.80-2.00 (m, 2H), 2.14 (s, 6H), 2.40-2.80 (m, 6H), 3.65 (d, 2H), 3.75-3.88 (m, 1H), 6.98-7.14 (m, 3H), 7.40-7.49 (m, 1H), 7.49-7.60 (m, 2H), 7.60-7.70 (m, 1H), 7.78 (d, 1H). m/s: 334.

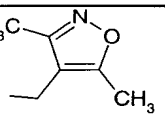
Examples 63-72

The compounds shown in Table 3 were made according to the procedure of Example 62.

Table 3

Ex	R^1	R^2	R^3	$(R^4)_r$	n	NMR	m/s
63[1]	Me	Me		H	1	1.42-1.68 (m, 2H), 1.80-2.00 (m, 2H), 2.08 (s, 3H), 2.10 (s,3H), 2.33-2.76 (m, 6H), 3.65-3.85 (m, 3H), 6.95-7.13 (m, 3H), 7.45-7.57 (m, 2H), 7.57-7.70 (m, 2H), 7.84 (d, 1H)	354
64[1]	Me	Me		H	1	1.47-1.67 (m, 2H), 1.83-1.98 (m, 2H), 2.12 (s, 3H), 2.14 (s, 3H), 2.40-2.80 (m, 6H), 3.56 (s, 2H), 3.77-3.87 (m, 1H), 6.97-7.12 (m, 3H), 7.48-7.68 (m, 5H)	377
65[1]	Me	Me		H	1	1.45-1.67 (m, 2H), 1.83-1.99 (m, 2H), 2.10 (s, 3H), 2.15 (s, 3H), 2.40-2.78 (m, 6H), 3.47 (s, 2H), 3.77-3.88 (m, 1H), 6.98-7.13 (m, 3H), 7.19-7.40 (m, 4H), 7.54-7.62 (m, 1H)	343

66[1]	Me	Me		H	1	1.46-1.68 (m, 2H), 1.85-1.98 (m, 2H), 2.11 (s, 3H), 2.15 (s, 3H), 2.38-2.80 (m, 6H), 3.43 (s, 2H), 3.70 (s, 3H), 3.77-3.88 (m, 1H), 6.74-6.89 (m, 3H), 6.98-7.12 (m, 3H), 7.16-7.24 (m, 1H), 7.53-7.62 (m, 1H)	339
67[1]	Me	Me		H	1	1.26 (s, 9H), 1.44-1.67 (m, 2H), 1.80-2.00 (m, 2H), 2.03-2.20 (m, 5H), 2.35-2.80 (m, 7H), 3.23-3.50 (m, 2H), 3.73-3.86 (m, 1H), 7.00-7.40 (m, 7H), 7.53-7.60 (m, 1H)	365
68[1]	Me	Me		H	1	1.45-1.68 (m, 2H), 1.83-2.00 (m, 2H), 2.13 (s, 3H), 2.16 (s, 3H), 2.40-2.80 (m, 6H), 3.61 (s, 2H), 3.77-3.88 (m, 1H), 6.98-7.15 (m, 3H), 7.48-7.62 (m, 3H), 8.13-8.23 (m, 2H)	354
69[1]	Me	Me		H	1	1.44-1.68 (m, 2H), 1.80-2.00 (m, 2H), 2.12 (s, 3H), 2.16 (s, 3H), 2.36-2.80 (m, 6H), 3.55 (s, 2H), 3.72-3.89 (m, 1H), 7.00-7.17 (m, 3H), 7.48 (d, 2H), 7.50-7.60 (m, 1H), 7.77 (d, 2H)	334
70[1]	Me	Me		H	1	1.48-1.68 (m, 2H), 1.85-1.98 (m, 2H), 2.13 (s, 3H), 2.16 (s, 3H), 2.43-2.80 (m, 6H), 3.20 (s, 3H), 3.58 (s, 2H), 3.79-3.87 (m, 1H), 6.98-7.13 (m, 3H), 7.50-7.62 (m, 3H), 7.82-7.90 (m, 2H)	387
71[1]	Me	Me		H	1	1.47-1.68 (m, 2H), 1.85-1.98 (m, 2H), 2.16 (s, 6H), 2.43-2.80 (m, 6H), 3.60 (s, 2H), 3.78-3.88 (m, 1H), 7.00-7.13 (m, 3H), 7.20-7.28 (m, 1H), 7.41 (d, 1H), 7.53-7.62 (m, 1H), 7.70-7.78 (m, 1H), 8.43-8.50 (m, 1H)	310

72[1]	Me	Me		H	1	1.48-1.67 (m, 2H), 1.83-1.98 (m, 2H), 2.06 (s, 3H), 2.13 (s, 3H), 2.14 (s, 3H), 2.28 (s, 3H), 2.33-2.80 (m, 6H), 3.15-3.24 (m, 2H), 3.77-3.87 (m, 1H), 6.98-7.17 (m, 3H), 7.50-7.60 (m, 1H)	328

[1] S Enantiomer

Example 73

1-{2-Piperidin-1-ylethyl[*N*-(3-phenylpropyl)]amino}-1,2,3,4-tetrahydronaphthalene.

1-Bromo-3-phenylpropane (296 µL, 1.93 mmol) was added to a solution of 1-(2-piperidin-1-ylethylamino)-1,2,3,4-tetrahydronaphthalene (Example 60) (500 mg, 1.93 mmol) in 3.9 mL of THF, followed by triethylamine (269 µL, 1.93 mmol) and the reaction was heated to reflux. After refluxing overnight, the reaction was still incomplete and an additional 296 µL of 1-bromo-3-phenylpropane and 269 µL of triethylamine was added and heating was continued for 4 days. The reaction mixture was cooled and solvents were removed in vacuo to yield an orange liquid. Purification by silica gel chromatography (30:1 dichloromethane:2M ammonia in methanol) afforded 258 mg of the desired product. ^{1}H NMR ($CDCl_3$): 7.76 (d, 1H), 7.32-7.02 (m, 8H), 3.95 (dd, 1H), 2.81-2.32 (m, 12H), 2.01 (m, 2H), 1.78 (m, 2H), 2.70-1.26 (m, 10H); m/s: 377.

Example 74

1-[2-(*N*-Phenethylpiperidin-4-ylamino)ethylamino]-1,2,3,4-tetrahydronaphthalene.

1-[2-(*N*-Phenethylpiperidin-4-ylamino)acetamido]-1,2,3,4-tetrahydronaphthalene (Example 118) (0.584g, 1.49×10^{-3} mole) was dissolved in tetrahydrofuran (10 mL) and treated with 1.0 M borane-tetrahydrofuran (13.0 mL, 1.30×10^{-2} mole) at ambient temperature. After one hour, xylene (30 mL) was added and the mixture was refluxed for 24 hours. The mixture was cooled to ambient temperature, quenched with 1M hydrochloric acid (30 mL), and stirred for 22 hours. The reaction mixture was partitioned between 1M sodium hydroxide and dichloromethane. The aqueous portion was extracted with additional dichloromethane. The combined organic portions were washed (brine), dried, and evaporated to yellow oil which was purified by chromatography, eluting with 1% ammonium hydroxide:10% methanol:89% methylene chloride (v/v/v), to give the product as a colourless oil (0.113g). ^{1}H NMR: 1.11-

1.31 (m, 2H), 1.52-2.06 (m, 10H), 2.24-2.94 (m, 13H), 3.64 (t, 1H), 7.00-7.40 (m, 9H); m/s: 378.

Example 75

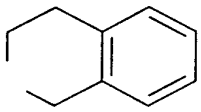
N-[2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethyl]-*N*-methyl-*N*-[(1*S*)-1,2,3,4-tetrahydronaphthalen-1-yl]amine bismaleate salt.

A solution of *N*-[2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethyl]-*N*-methyl-*N*-[(1*S*)-1,2,3,4-tetrahydronaphthalen-1-yl]amine (see Example 6) (3.96g, 1.23×10^{-2} mole) in diethyl ether (20 mL) was added to a stirring solution of maleic acid (3.13g, 2.70×10^{-2} mole) in diethyl ether (350 mL). The salt form immediately precipitated, adhering to the sides of the flask to form a gum. After solidification upon standing overnight, the material was collected by vacuum filtration. The solid was re-suspended in fresh diethyl ether, stirred and sonicated, and collected by vacuum filtration. The solid was vacuum dried at 50 °C for four hours, then ground to a fine powder. Drying was continued at 50 °C for 16 hours to give the product as a white solid (6.35g, 93%). ^{1}H NMR: 1.55-1.83 (m, 2H), 1.90-2.09 (m, 2H), 2.36 (s, 3H), 2.62-2.92 (m, 3H), 3.00-3.38 (m, 3H), 4.13-4.27 (m, 7H), 7.57-7.63 (m, 1H); m/s: 321.

Examples 76-82

Bismaleate salts of the following compounds according to formula XXIII were prepared using the procedure of Example 73. The examples shown in Table 4 are provided by way of illustration and not by way of limitation.

Table 4

Ex	R^1	R^2	R^3	$(R^4)_r$	n	NMR	m/s
76[2]	Me	Et	Et	H	1	1.16 (t, 6H), 1.52-1.70 (m, 2H), 1.85-2.00 (m, 2H), 2.17 (s, 3H), 2.60-2.94 (m, 4H), 3.05-3.30 (m, 6H), 3.92-4.02 (m, 1H), 6.14 (s, 4H), 7.02-7.22 (m, 3H), 7.57-7.65 (m, 1H)	261
77[2]	Me			H	1	1.53-2.10 (m, 4H), 2.36 (s, 3H), 2.64-2.91 (m, 3H), 3.00-3.10 (m, 4H), 3.16-3.80 (m, 3H), 4.14-4.27 (m, 3H), 6.14 (s, 4H), 7.08-7.33 (m, 7H), 7.58-7.63 (m, 1H)	321
78	H	$-(CH_2)_5-$		5-Me, 8-Me	1	1.52 (m, 2H), 1.67 (m, 6H), 1.85 (m, 2H), 2.15 (s, 3H), 2.21 (m, 1H), 2.35 (s, 3H), 2.47 (m, 1H), 2.72 (dd, 1H), 3.04-3.22 (m, 8H), 4.23 (br s, 1H), 6.10 (s, 4H), 6.99 (d, 1H), 7.06 (d, 1H)	287
79[1]	Me	$-(CH_2)_5-$		H	1	1.47-1.80 (m, 8H), 1.85-2.00 (m, 2H), 2.19 (s, 3H), 2.60-2.90 (m, 4H), 3.03-3.28 (m, 6H), 3.91-4.03 (m, 1H), 6.14 (s, 4H), 7.03-7.21 (m, 3H), 7.56-7.61 (m,1H)	273
80[1]	H	$-(CH_2)_6-$		H	1	1.52-2.09 (m, 12H), 2.65-2.92 (m, 2H), 3.02-3.35 (m, 9H), 4.23-4.37 (m, 1H), 6.08 (s, 4H), 7.14-7.36 (m, 3H), 7.42-7.52 (m, 1H)	273
81[1]	Me	Me	$-(CH_2)_2Ph$	H	1	1.53-1.75 (m, 2H), 1.87-2.00 (m, 2H), 2.18 (s, 3H), 2.63-3.03 (m, 9H), 3.20-3.38 (m, 4H), 3.97-4.06 (m, 1H), 6.14 (s, 4H), 7.04-7.42 (m, 8H), 7.56-7.62 (m, 1H)	323
82[1]	H	Me	$-CH_2Ph$	H	1	1.67-2.16 (m, 4H), 2.32 (s, 3H), 2.67-2.92 (m, 5H), 3.10-3.20 (m, 2H), 3.73-3.82 (m, 2H), 4.40-4.47 (m, 1H), 6.12 (s, 4H), 7.18-7.52 (m, 9H)	295

[1] S Enantiomer
[2] R Enantiomer

Example 83

N-methyl-*N*-(2-{methyl[(1*S*)-1,2,3,4-tetrahydro-1-naphthalenyl]amino}ethyl)benzenesulfonamide.

A solution of the compound of Example 123 (1.61g, 4.32×10^{-3} mole) was treated in THF (36 mL) with lithium aluminum hydride (0.66g, 1.74×10^{-3} mole). After refluxing for two hours, the mixture was quenched with sodium sulfate decahydrate until effervescence ceased. Additional THF and diethyl ether were added to aid stirring. The quenched mixture was filtered through diatomaceous earth and the filtrate evaporated to a solid/oil mixture which was purified by chromatography, eluting with 3:1 hexane/ethyl acetate (v/v), to give the title compound as a pale yellow oil (0.92 g, 59%). ^{1}H NMR: 1.42-1.68 (m, 2H), 1.82-1.97 (m, 2H), 2.17 (s, 3H), 2.47-2.59 (m, 2H), 2.66 (s, 5H), 2.96-3.20 (m, 2H), 3.78-3.85 (m, 1H), 7.00-7.16 (m, 3H), 7.50-7.80 (m, 6H). m/s: 359.

Example 84

2-{5-[methyl(2-piperidinoethyl)amino]}-5,6,7,8-tetrahydro-2-naphthalenyl-2-propanol.

A solution of t-butyllithium (1.7M in pentane, 700 µL, 1.19 mmol) was added to THF which had been precooled to -78 °C and a bright yellow solution was obtained. A precooled solution of the compound of Example 19 (200 mg, 0.569 mmol) in 1.4 mL of THF was then added. Additional t-butyllithium (1.7M in pentane, 500 µL, 0.850 mmol) was added to ensure complete metal-halogen exchange. After 10 min, acetone (420 µL, 5.69 mmol) in 1 mL of THF was added and the reaction turned bright yellow. After 30 min, another 420 µL of acetone was added.

The reaction was then stirred at -78 °C for 2h and allowed to warm slowly to -20 °C. It was quenched after 3h by addition to saturated NH_4Cl solution (6 mL). The product was then extracted with ether (2 x 5mL). The organic extracts were washed with brine (1 x 20 mL) and dried over Na_2SO_4. Removal of solvents gave a yellow oil which was purified by silica gel chromatography (20:1 methylene chloride/ 2M ammonia in methanol then 10:1 methylene chloride/2M ammonia in methanol). The title compound was obtained as a thick gum (97 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.43 (m, 2H), 1.51-1.67 (m, 13H), 1.99 (m, 2H), 2.27 (s, 3H), 2.33-2.69 (m, 8H), 2.72 (m, 2H), 3.86 (m, 1H), 7.17 (s, 1H), 7.24 (m, 1H), 7.64 (m, 1H). m/s = 331.

Example 85

6-Isopropenyl-*N*-methyl-*N*-(2-piperidinoethyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

6-Isopropenyl-*N*-methyl-*N*-(2-piperidinoethyl)-1,2,3,4-tetrahydro-1-naphthalenamine was made by adding titanium(IV) chloride (1.0M in methylene chloride, 267 µL, 0.267 mmol) to a solution of a compound of Example 80 (88 mg, 0.267 mmol) in 5.3 mL of methylene chloride at -30 to -40 °C. A light brown suspension was obtained. After 10 min, dimethylzinc (2.0 M in toluene, 133.5 µL, 0.267 mmol) was added.

A dark brown suspension was obtained. This was stirred for 1h. The reaction was then allowed to warm to room temperature slowly. The reaction mixture was then added to water (6 mL) and methylene chloride (4 mL). An emulsion was formed and so ether was added. The layers were separated. The aqueous layer was acidified with 1N HCl solution and stirred for 3h. Then the pH was adjusted to 14 by addition of 1N NaOH solution. It was then extracted with methylene chloride. The organic extracts were then washed with brine and dried over Na_2SO_4. Removal of solvents yielded a residue which was purified by silica gel chromatography (15:1 methylene chloride/ 2M ammonia in methanol) to afford the title compound (10 mg). ^{1}H NMR (300 MHz, $CDCl_3$): 1.42 (m, 2H), 1.53 -1.70 (m, 6H), 1.99 (m, 2H), 2.13 (s, 3H), 2.27 (s, 3H), 2.37 (m, 4H), 2.42 - 2.70 (m, 4H), 2.72 (m, 2H), 3.86 (m, 1H), 5.03 (m, 1H), 5.34 (m, 1H), 7.14 (m, 1H), 7.28 (m, 1H), 7.64 (m, 1H). m/s: 313.

Example 86

6-(*Tert*-butyl)-*N*-methyl-*N*-(2-piperidinoethyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

6-(*Tert*-butyl)-*N*-methyl-*N*-(2-piperidinoethyl)-1,2,3,4-tetrahydro-1-naphthalenamine was made by adding dimethylzinc (2.0M in toluene, 133.5 µL, 0.267 mmol) to a solution of titanium(IV) chloride (1.0M in methylene chloride, 267 µL, 0.267 mmol) in 0.6 mL of methylene chloride at -30 °C, and stirring the resulting orange suspension for 30 min. A solution of a compound according to Example 80 (44 mg, 0.133 mmol) in 0.6 mL of methylene chloride was added dropwise. An additional 0.6 mL of methylene chloride was used to ensure complete transfer of the compound. The reaction mixture turned dark brown. It was allowed to warm up to room temperature slowly. After 4h, the reaction was quenched by addition to NH_4Cl solution and the product was extracted with methylene chloride (3 x 5 mL). The combined organics were washed with brine (1 x 10 mL) and dried over Na_2SO_4.

Solvents were removed to yield a residue. Silica gel chromatography (15:1 methylene chloride/2M ammonia in methanol) yielded the title compound (6 mg, 13%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.30 (s, 9H), 1.45 (m, 2H), 1.56 (m, 4H), 1.66 (m, 2H), 1.98 (m, 2H), 2.27 (s, 3H), 2.41-2.68 (m, 4H), 2.70 (m, 2H), 3.85 (m, 1H), 7.03 (s, 1H), 7.17 (m, 1H), 7.58 (m, 1H). m/s: 329.

Preparation of Starting Materials

The following reactions (Examples 87-135) are provided to illustrate but not limit methods for the preparation of intermediate materials used to make compounds of the invention.

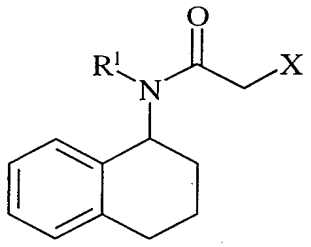
Example 87

(S)-1-(*N*-methyl-2-chloroacetamido)-1,2,3,4-tetrahydronaphthalene.

(S)-1-methylamino-1,2,3,4-tetrahydronaphthalene (Smith, R.A.; White, R.L.; Krantz, A., *J. Med. Chem.*, (1988), *31*, 1558-66) (3.02g, 1.87×10^{-2} mole) and 1,8-bis(dimethylamino)naphthalene (6.59g, 3.07×10^{-2} mole) were combined in dichloromethane (52 mL) and cooled to 0 °C (ice/water/sodium chloride). Chloroacetyl chloride (2.4 mL, 3.01×10^{-2} mole) was added in small portions, maintaining the reaction temperature at < 10 °C. Upon complete addition, the mixture was slowly warmed to ambient temperature over 1.5 hours by melting of the bath. The product was partially purified by chromatography of the reaction mixture with 3:1 hexane:ethyl acetate (v/v), to give the title product as a yellow oil (4.58g). ^{1}H NMR: 1.67-2.16 (m, 4H), 2.67-2.84 (m, 5H), 4.43-4.57 (m, 2H), 5.05-5.15 (m, 0.3H), 5.60-5.71 (m, 0.7H), 6.90-7.23 (m, 4H).

Examples 88-91

Compounds of formula XXV shown in Table 5, were prepared using the procedure of Example 87, described above.



XXV

Table 5

Ex	R^1	X	NMR
88	Me	Cl	1.64-2.16 (m, 4H), 2.64-2.90 (m, 5H), 4.40-4.60 (m, 2H), 5.06-5.15 (m, 0.3H), 5.60-5.70 (m, 0.7H), 6.92-7.24 (m, 4H)
89[2]	H	Cl	1.62-1.96 (m, 4H), 2.63-2.83 (m, 2H), 4.08 (d, 2H), 4.90-5.02 (m, 1H), 7.06-7.23 (m, 4H), 8.60 (d, 1H)
90[1]	H	Cl	1.60-1.96 (m, 4H), 2.62-2.83 (m, 2H), 4.08 (d, 2H), 4.90-5.00 (m, 1H), 7.07-7.24 (m, 4H), 8.61 (d, 1H)
91	H	Br	1.60-1.97 (m, 4H), 2.63-2.83 (m, 2H), 3.88 (d, 2H), 4.87-5.00 (m, 1H), 7.04-7.24 (m, 4H), 8.68 (d, 1H)

[1] S Enantiomer
[2] R Enantiomer

The starting material for Examples 88-91 is described in Smith, R.A.; White, R.L.; Krantz, A., *J. Med. Chem.*, (1988), *31*, 1558-66, which description is incorporated herein by reference.

Example 92

(S)-1-[2-(1,2,3,4-tetrahydroisoquinolin-2-yl)-*N*-methyl-acetamido]-1,2,3,4-tetrahydro naphthalene.

(S)-1-(*N*-methyl-2-chloroacetamido)-1,2,3,4-tetrahydronaphthalene (prepared by Example 87) (4.58 g, 1.93×10^{-2} mole) and 1,2,3,4-tetrahydroisoquinoline (7.74 g, 5.81×10^{-2} mole) were combined in acetonitrile (110 mL) and heated at reflux for 14.5 hours. The solvent was evaporated and the residue partitioned between aqueous sodium bicarbonate and ethyl acetate. The aqueous portion was extracted with additional ethyl acetate. The combined extracts were washed (water, brine), dried, and evaporated to yield a residue which was purified by chromatography, eluting with 1:1 hexane:ethyl acetate (v/v), to give the title product as a yellow oil (5.88 g). ^{1}H NMR: 1.62-2.05 (m, 4H), 2.48 (s, 1H), 2.60-2.92 (m, 8H), 3.35-3.80 (m, 4H), 5.36-5.45 (m, 0.5H), 5.66-5.76 (m, 0.5H), 6.86-7.20 (m, 8H).

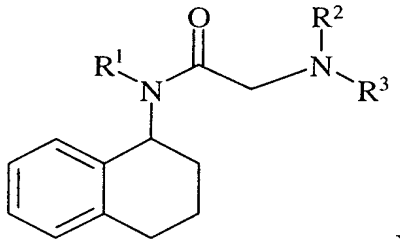
Example 93

(*R*)-1-(2-Diethylaminoacetamido)-1,2,3,4-tetrahydronaphthalene.

(*R*)-1-(2-Chloroacetamido)-1,2,3,4-tetrahydronaphthalene (prepared by the method of Example 89) (4.00g, $1.79x10^{-2}$ mole) and diethylamine (5.0 mL, $4.83x10^{-2}$ mole) were combined in acetonitrile (100 mL) and heated at 90 °C for 4 hours. The reaction mixture was evaporated and partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The aqueous portion was extracted with additional ethyl acetate. The combined organic extracts were washed (water, brine), dried, and evaporated to give the product as a brown oil (4.59 g). ^{1}H NMR: 0.94 (t, 6H), 1.68-1.95 (m, 4H), 2.63-2.87 (m, 2H), 2.98 (m, 2H), 4.91-5.04 (m, 1H), 7.03-7.20 (m, 4H), 7.82 (d, 1H). m/s: 261.

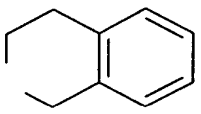
Examples 94 - 121

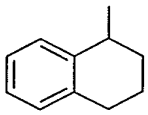
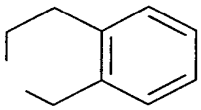
The compounds of formula XXVI shown in Table 6, were prepared using a procedure analogous to that described in Example 92 or 93.

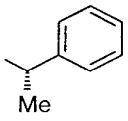
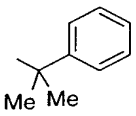
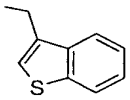
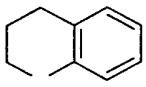


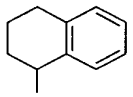
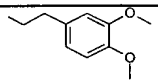
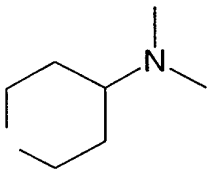
XXVI

Table 6

Ex	R^1	R^2	R^3	M*	NMR	m/s
94[1]	H	Me	-CH_2Ph	93	1.65-1.95 (m, 4H), 2.19 (s, 3H), 2.66-2.87 (m, 2H), 3.03 (s, 2H), 3.58 (s, 2H), 4.95-5.07 (m, 1H), 7.04-7.40 (m, 9H), 8.01 (d, 1H)	309
95[2]	H	Me	-CH_2Ph	93	1.64-2.00 (m, 4H), 2.19 (s, 3H), 2.63-2.87 (m, 2H), 3.03 (s, 2H), 3.58 (s, 2H), 4.94-5.07 (m, 1H), 7.03-7.42 (m, 9H), 8.01 (d, 1H)	309
96[1]	H			93	1H NMR **$CDCl_3$**: 1.82 (m, 3H), 2.07 (m, 1H), 2.82 (m, 6H), 3.25 (s, 2H), 3.49 (d, J = 6Hz, 1H), 3.72 (s, 2H), 5.24 (m, 1H), 6.98 (m, 1H), 7.15 (m, 6H), 7.47 (m, 1H)	321

97	H	H	-CH_2Ph	93	1.60-1.97 (m, 4H), 2.61-2.80 (m, 3H), 3.13 (s, 2H), 3.67 (s, 2H), 4.94-5.05 (m, 1H), 7.04-7.40 (m, 9H), 8.09 (d, 1H)	295
98	H	H		93	1.50-2.00 (m, 8H), 2.32-2.48 (m, 1H), 2.58-2.83 (m, 4H), 3.21 (s, 2H), 3.60-3.73 (m, 1H), 4.93-5.07 (m, 1H), 7.00-7.40 (m, 8H), 8.14 (d, 1H)	M+23=357
99[2]	H	-$(CH_2)_5$-		93	1.30-1.57 (m, 6H), 1.67-1.97 (m, 4H), 2.30-2.43 (m, 4H), 2.63-2.82 (m, 2H), 2.92 (s, 2H), 4.93-5.04 (m, 1H), 7.06-7.20 (m, 4H), 7.83 (d, 1H)	273
100[2]	H			93	1.64-2.00 (m, 4H), 2.63-2.98 (m, 6H), 3.18 (s, 2H), 3.66 (s, 2H), 4.98-5.08 (m, 1H), 7.00-7.27 (m, 8H), 8.02 (d, 1H)	321
101[1]	Me	Me	-CH_2Ph	92	1.57-2.01 (m, 4H), 2.17-2.27 (m, 3H), 2.45 (s, 1.2H), 2.63-2.87 (m, 3.8H), 3.23-3.69 (m, 4H), 5.20-5.32 (m, 0.4H), 5.63-5.76 (m, 0.6H), 6.85-7.02 (m, 1H), 7.04-7.42 (m, 8H)	323
102[1]	Me	-CH_2CH_3	-CH_2Ph	92	0.96-1.10 (m, 3H), 1.44-2.00 (m, 4H), 2.40-2.84 (m, 7H), 3.20-3.78 (m, 4H), 5.13-5.23 (m, 0.5H), 5.63-5.73 (m, 0.5H), 6.81-6.98 (m, 1H), 7.02-7.43 (m, 8H)	337
103[1]	Me	-CH_2CH_2-OH	-CH_2Ph	92	1.52-2.02 (m, 4H), 2.40-2.87 (m, 7H), 3.36-3.86 (m, 6H), 4.50-4.60 (m,1H), 5.11-5.20 (m, 0.4H), 5.63-5.74 (m, 0.6H), 6.83-6.97 (m, 1H), 7.03-7.44 (m, 8H)	353
104[1]	Me	-CH_2CH_2-$N(Me)_2$	-CH_2Ph	92	1.53-1.98 (m, 4H), 2.02-2.15 (m,6H), 2.29-2.85 (m, 9H), 3.30-3.82 (m, 4H), 5.22-5.32 (m, 0.4H), 5.62-5.73 (m, 0.6H), 6.84-7.00 (m, 1H), 7.03-7.43 (m, 8H)	380

105[1]	Me	$-CH_2CH_2-CH_3$	$-CH_2Ph$	92	0.73-0.88 (m, 3H), 1.40-2.00 (m, 6H), 2.37-2.85 (m, 7H), 3.22-3.41 (m, 2H), 3.50-3.78 (m,2H), 5.10-5.22 (m, 0.5H), 5.60-5.72 (m, 0.5H), 6.84-6.97 (m, 1H), 7.03-7.40 (m, 8H)	351
106[1]	Me	$-CH_2-(CH_2)_2CH_3$	$-CH_2Ph$	92	0.83 (t, 3H), 1.18-1.35 (m, 2H), 1.35-2.00 (m, 6H), 2.37-2.84 (m, 7H), 3.23-3.40 (m, 2H), 3.49-3.78 (m, 2H), 5.11-5.24 (m, 0.4H), 5.60-5.73 (m, 0.6H), 6.83-6.98 (m, 1H), 7.03-7.42 (m, 8H)	365
107[1]	Me	Me		92	1.23-1.40 (m, 3H), 1.60-2.02 (m, 4H), 2.12-2.27 (m, 3H), 2.43 (s, 1.4H), 2.60-2.87 (m, 4H), 3.25 (s, 1.6H), 3.71-3.88 (m, 1H), 5.16-5.27 (m, 0.4H), 5.61-5.73 (m, 0.6H), 6.83-6.96 (m, 1H), 7.02-7.43 (m, 8H)	337
108[1]	Me	H		92	1.32-1.49 (m, 6H), 1.61-2.00 (m, 4H), 2.40-2.83 (m, 6H), 3.07-3.37 (m, 2H), 4.87-4.98 (m, 0.3H), 5.63-5.74 (m, 0.7H), 6.71-6.87 (m, 1H), 7.02-7.52 (m, 8H)	337
109[1]	Me	Me		92	0.90-1.11 (m, 0.5H), 1.53-2.01 (m, 3.5H), 2.22-2.82 (m, 7.5H), 3.11-3.46 (m, 2.5H), 3.62-3.72 (m, 0.5H), 3.81-3.95 (m, 1.5H), 4.95-5.06 (m, 0.5H),5.66-5.80 (m, 0.5H), 6.84-7.02 (m, 1.5H), 7.04-7.20 (m, 3H), 7.22-7.32 (m, 0.5H), 7.33-7.40 (m, 1H), 7.59 (d, 1H), 7.72 (d, 0.5H), 7.89-8.02 (m, 1H), 8.05-8.13 (m, 0.5H)	379
110	Me			92	1.60-2.17 (m, 6H), 2.60-2.90 (m, 6H), 2.43-2.56 (m, 1H), 3.20-3.43 (m, 2H), 4.04-4.60 (m, 2H), 5.04-5.23 (m, 0.3H), 5.60-5.73 (m,0.7H), 6.36-6.54 (m, 2H), 6.80-7.28 (m, 6H)	335
111[1]	H	$-(CH_2)_6-$		93	1.42-1.98 (m, 12H), 2.57-2.83 (m, 6H), 3.12 (s, 2H), 4.93-5.06 (m, 1H), 7.05-7.22 (m, 4H), 7.78-7.88 (m, 1H)	287

112	Me	-$(CH_2)_6$-		92	1.43-2.13(m, 12H), 2.40-2.86 (m, 9H), 3.25-3.46 (m, 2H), 5.36-5.45 (m, 0.5H), 5.62-5.74 (m, 0.5H), 6.85-7.23 (m, 4H)	301
113	Me	Me		92	1.49-2.04 (m, 8H), 2.07-2.32 (m, 3H), 2.46-2.87 (m, 7H), 3.17-3.69 (m, 2H), 2.80-4.03 (m, 1H), 4.81-5.77 (m, 1H), 6.75-7.72 (m, 8H)	363
114[1]	H	-$(CH_2)_5$-		93	1.27-1.59 (m, 6H), 1.65-1.97 (m, 4H), 2.34-2.48 (m, 4H), 2.62-2.83 (m, 2H), 2.88-3.00 (m, 2H), 4.92-5.03 (m, 1H), 7.05-7.22 (m, 4H), 7.80-7.92 (m, 1H)	273
115[1]	Me	-$(CH_2)_5$-		92	1.27-1.60 (m, 6H), 1.62-2.12 (m, 4H), 2.27-2.87 (m, 9H), 3.07-3.44 (m, 2H), 5.33-5.46 (m, 0.5H), 5.60-5.72 (m, 0.5H), 6.83-7.22 (m, 4H)	287
116[1]	Me	Me	-$(CH_2)_2$Ph	92	1.44-2.02 (m, 4H), 2.29 (s, 1H), 2.34 (s, 2H), 2.43 (s, 1H), 2.56-2.87 (m, 8H), 3.21-3.38 (m, 2H), 5.24-5.35 (m, 0.6H), 5.60-5.72 (m, 0.4H), 6.84-7.33 (m, 9H)	337
117[2]	H	Me	-$(CH_2)_2$Ph	93	1.51-1.90 (m, 4H), 2.29 (s, 3H), 2.53-2.83 (m, 6H), 3.04 (s, 2H), 4.90-5.00 (m, 1H), 7.04-7.23 (m, 9H), 7.57 (d, 1H)	323
118[1]	H	Me	-$(CH_2)_2$Ph	93	1.52-1.90 (m, 4H), 2.29 (s, 3H), 2.55-2.80 (m, 6H), 3.05 (s, 2H), 4.89-5.02 (m, 1H), 7.03-7.21 (m, 9H), 7.53-7.63 (m, 1H)	323
119[1]	Me	Me		92	1.43-2.00 (m, 4H), 2.25-2.45 (m, 4H), 2.56-2.83 (m, 8H), 3.20-3.40 (m, 2H), 3.60-3.77 (m, 6H), 5.24-5.37 (m, 0.4H), 5.60-5.71 (m, 0.6H), 6.60-7.00 (m, 4H), 7.05-7.20 (m, 3H)	397
120[1]	Me			92	1.15-1.48 (m, 2H), 1.65-2.10 (m, 9H), 2.13 (s, 3H), 2.18 (s, 3H), 2.45 (s, 1.5H), 2.63-3.00 (m, 5.5H), 3.10-3.40 (m, 2H), 5.32-5.41 (m, 0.5H), 5.60-5.73 (m, 0.5H), 6.83-7.20 (m, 4H))	330

121[1]	Me	$-(CH_2)_4-$	92	$CDCl_3$ 1.72-1.89 (m, 6H), 1.97-2.05 (m, 2H), 2.55-2.86 (m, 7H), 3.40 (m, 2H), 3.49 (s, 1H), 5.37 (m, 1H), 5.93 (m, 1H), 6.98-7.20 (m, 4H)	273

[1] S Enantiomer
[2] R Enantiomer
M* made by method of Example number

Example 122

N^1,N^2-dimethyl-N^1-[(1*S*)-1,2,3,4-tetrahydro-1-naphthalenyl]-1,2-ethanediamine.

A suspension of *N*-(*t*-butoxycarbonyl)glycine (2.26g, $1.29x10^{-2}$ mole) and 1-hydroxybenzotriazole (1.77g, $1.31x10^{-2}$ mole) in DCM (40 mL) was treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.86 g, $1.49x10^{-2}$ mole). The coupling agent was washed in with DCM (10mL), then triethylamine (2.1 mL, $1.51x10^{-2}$ mole) was added. Immediately, a solution of *(S)*-1-methylamino-1,2,3,4-tetrahydronaphthalene (Smith, R.A.; White, R.L.; Krantz, A., *J. Med. Chem.*, (1988), *31*, 1558-66) (1.95g, $1.21x10^{-2}$ mole) in DCM (50 mL) was added. After stirring at ambient temperature for 19 hours, the reaction mixture was partitioned between water and DCM. The aqueous portion was extracted with additional DCM. The combined organic portions were washed (water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1:1 hexane/ethyl acetate (v/v) to give the product as a pale yellow oil (3.40 g, 88%). ^{1}H NMR: 1.30-1.50 (m, 9H), 1.65-2.02 (m, 4H), 2.48 (s, 1H), 2.61 (s, 2H), 2.67-2.86 (m, 2H), 3.77-4.00 (m, 2H), 5.00-5.12 (m, 0.4H), 5.63-5.73 (m, 0.6H), 6.73-7.01 (m, 2H), 7.05-7.22 (m, 3H).

A solution of the oil (3.40 g, $1.07x10^{-2}$ mole) in THF (80 mL) was treated with lithium aluminum hydride (1.63 g, $4.30x10^{-2}$ mole) and refluxed for two hours. The reaction mixture was quenched with sodium sulfate decahydrate until effervescence ceased. Additional THF and diethyl ether were added to aid stirring. The quenched mixture was filtered through diatomaceous earth and the filtrate evaporated to a yellow oil which was purified by chromatography, eluting with 10% 2.0M NH_3 in MeOH: 90% DCM (v/v), to give the title compound as a pale yellow oil (2.24 g, 96%). ^{1}H NMR: 1.50-1.67 (m, 2H), 1.83-1.98 (m, 2H), 2.14 (s, 3H), 2.26 (s, 3H), 2.41-2.77 (m, 6H), 3.13-3.50 (m, 1H), 3.76-3.85 (m, 1H), 6.96-7.18 (m, 3H), 7.58 (d, 1H). m/s: 219.

Example 123

N-Methyl-2-[methyl(phenylsulfonyl)amino]-*N*-[(1*S*)-1,2,3,4-tetrahydro-1-naphthalenyl]acetamide.

A suspension of *N*-phenylsulfonylsarcosine (1.00, 4.35×10^{-3} mole) and 1-hydroxybenzotriazole (0.63 g, 4.69×10^{-3} mole) in DCM (15 mL) was treated with 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride (1.03 g, 5.38×10^{-3} mole). The coupling agent was washed in with DCM (3 mL), then triethylamine (0.73 mL, 5.24×10^{-3} mole) was added. Immediately, a solution of *(S)*-1-methylamino-1,2,3,4-tetrahydronaphthalene (Smith, R.A.; White, R.L.; Krantz, A., *J. Med. Chem.*, (1988), *31*, 1558-66) (0.70 g, 4.33×10^{-3} mole) in DCM (18 mL). After stirring at ambient temperature for 18 hours, the reaction mixture was partitioned between water and DCM. The aqueous portion was extracted with additional DCM. The combined organic portions were washed (aqueous sodium bicarbonate, water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1:1 hexane/ethyl acetate (v/v) to give the title compound as a pale yellow oil (1.61 g, 100%). ^{1}H NMR: 1.62-2.07 (m, 4H), 2.48 (s, 1H), 2.57-2.85 (m, 7H), 4.06-4.20 (m, 2H), 5.10-5.20 (m, 0.3H), 5.56-5.68 (m, 0.7H), 6.88-7.04 (m, 1H), 7.07-7.24 (m, 3H), 7.55-7.75 (m, 3H), 7.80-7.91 (m, 2H). m/s: 373.

Example 124

1-[2-(*N*-Phenethylpiperidin-4-ylamino)acetamido]-1,2,3,4-tetrahydronaphthalene.

1-(2-aminoacetamido)-1,2,3,4-tetrahydronaphthalene (Czech. Patent Application No. CS 71-7151) (0.355g, 1.74×10^{-3} mole) and *N*-phenethyl-4-piperidone (0.361g, 1.77×10^{-3} mole) were combined in dichloromethane (5 mL) and treated with glacial acetic acid (0.100 mL, 1.75×10^{-3} mole). After stirring at ambient temperature for ten minutes, sodium triacetoxyborohydride (0.570g, 2.69×10^{-3} mole) was added along with additional methylene chloride (5 mL) and stirring continued for 65 hours. The reaction mixture was partitioned between 0.1 M sodium hydroxide and methylene chloride. The aqueous portion was extracted with additional dichloromethane. The combined organic portions were washed (water, brine), dried, and evaporated to a brown oil which was purified by chromatography, eluting with 1% ammonium hydroxide:5% methanol: 94% methylene chloride (v/v/v), to give the title compound as a yellow oil (0.613 g). ^{1}H NMR: 1.10-1.33 (m, 2H), 1.60-2.02 (m, 8H), 2.07-

2.92 (m, 10H), 3.15 (s, 2H), 4.94-5.05 (m, 1H), 7.04-7.34 (m, 9H), 8.07 (d, 1H); m/s: 392, M+23$^+$ 414.

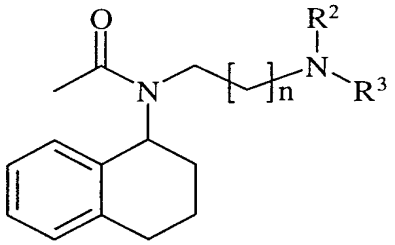
Example 125

1-[3-(4-methylpiperazin-1-yl)propyl(*N*-acetyl)amino]-1,2,3,4-tetrahydronaphthalene.

1-[3-(4-methylpiperazin-1-yl)propylamino]-1,2,3,4-tetrahydronaphthalene (Example 130) (0.292g, 1.02x10^{-3} mole) and triethylamine (0.500 mL, 3.59x10^{-3} mole) were combined in dichloromethane (8 mL) and treated with acetyl chloride (0.185 mL, 2.60x10^{-3} mole). The mixture was stirred at ambient temperature for 14 hours. The reaction mixture was partitioned between water and dichloromethane. The aqueous portion was extracted with additional dichloromethane. The combined extracts were washed (water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1% NH_4OH: 5% MeOH: 94% CH_2Cl_2 (v/v/v), to give the product as a colourless oil (0.317 g, 94%). ^{1}H NMR: 1.42-2.40 (m, 2H), 2.66-2.94 (m, 3H), 3.07-3.40 (m, 2H), 4.95-5.05 (m, 0.5H), 5.53-5.63 (m, 0.5H), 6.86-7.20 (m, 4H); m/s: 330.

Examples 126-127

The compounds of formula XXVII shown in Table 7, were prepared by the procedure of Example 125.



XXVII

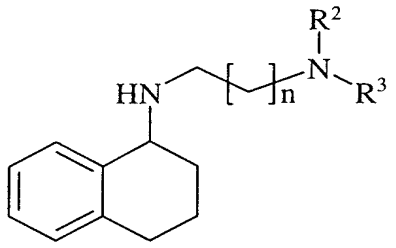
Table 7

Ex	R^2	R^3	n	NMR	m/s
126	-nBu	-nBu	2	0.74-0.86 (m, 6H), 1.08-1.32 (m, 8H), 1.37-2.30 (m, 15H), 2.54-3.28 (m, 4H), 4.96-5.05 (m, 0.5H), 5.56-5.67 (m, 0.5H), 6.85-7.22 (m, 4H)	359

127	$-(CH_2)_5-$	1	$CDCl_3$: 1.39 (m, 2H), 1.49 (m, 4H), 1.75-2.09 (m, 4.5H), 2.18 (s, 1.5H), 2.26 (s, 1.5H), 2.32-2.47 (m, 5H), 2.69 (td, 0.5H), 2.81 (m, 2.5H), 3.06 (m, 0.5H), 3.33 (m, 0.5H), 3.54 (m, 0.5H), 4.92 (dd, 0.5H), 5.84 (m, 0.5H), 7.19 - 6.95 (m, 4H)	301

Examples 128-133

The compounds of formula XXVIII shown in Table 8, were prepared using the procedure of Example 1.



XXVIII

Table 8

Ex	R^2	R^3	n	NMR	m/s
128	Me	Me	1	$CDCl_3$: 1.68-2.01 (m, 5H), 2.22 (s, 6H), 2.43 (t, 2H), 2.76 (m, 4H), 3.77 (t, 1H), 7.03-7.26 (m, 3H), 7.31 (m, 1H)	219
129	Me	Me	2	$CDCl_3$: 1.70 (m, 3H), 1.87 (m, 3H), 2.23 (s, 6H), 2.34 (m, 2H), 2.78 (m, 4H), 3.76 (t, 1H), 7.01-7.21 (m, 3H), 7.29(m, 1H)	233
130	$-(CH_2)_2N(Me)(CH_2)_2-$		2	1.46-2.00 (m, 8H), 2.12 (s, 3H), 2.14-2.80 (m, 13H), 3.61 (t, 1H), 6.97-7.18 (m, 3H), 7.28-7.40 (m, 1H)	288
131	-nBu	-nBu	2	0.85 (t, 6H), 1.15-2.00 (m, 15H), 2.13-2.80 (m, 10H), 3.57-3.64 (m, 1H), 7.00-7.15 (m, 3H), 7.30-7.38 (m, 1H)	317
132	-nBu	-nBu	1	0.85 (t, 6H), 1.17-1.43 (m, 9H), 1.53-2.00 (m, 5H), 2.23-2.80 (m, 9H), 3.63 (t, 1H), 7.00-7.17 (m, 3H), 7.22-7.34 (m, 1H)	303

133	$-(CH_2)_4CH(Me)-$	3	0.97 (d, 3H), 1.06-2.06 (m, 15H), 2.10-2.29 (m, 2H), 2.43-2.82 (m, 5H), 3.61 (t, 1H), 7.00-7.17 (m, 3H), 7.30-7.40 (m, 1H)	287

Example 134

N-Methyl-3-piperidino-*N*-[(1*S*)-1,2,3,4-tetrahydro-1-naphthalenyl]propanamide.

N-Methyl-3-piperidino-*N*-[(1*S*)-1,2,3,4-tetrahydro-1-naphthalenyl]propanamide was made by adding a solution of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (2.85 g, 14.9 mmol) and triethylamine (2.1 mL, 14.9 mmol) in 50 mL of dichloromethane to a solution of 1-piperidinepropionic acid (2.14 g, 13.6 mmol) and 1-hydroxybenzotriazole hydrate (1.84 g, 13.6 mmol) in 50 mL of dichloromethane. This was followed immediately by the addition of (*S*)-1-methylamino-1,2,3,4-tetrahydronaphthalene (2.00 g, 12.4 mmol) in 50 mL of dichloromethane. The reaction was then stirred at room temperature for 22 hours. The reaction was then added to water (150 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organics were washed with brine (1 x 250 mL) and dried over Na_2SO_4. Removal of solvents yielded a yellow liquid. Purification by silica gel chromatography (20:1 dichloromethane/2M ammonia in methanol) yielded the title compound (2.83 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (m, 2H), 1.57 (m, 4H), 1.71-2.03 (m, 4H), 2.46 (m, 4H), 2.60-2.80 (m, 7H), 3.49 (m, 1H), 5.08 (m, 1H), 5.94 (m, 1H), 6.99-7.18 (m, 4H). m/s $(M+1)^+$=301.

Example 135

N-Methyl-3-piperidino-*N*-[(1*R*)-1,2,3,4-tetrahydro-1-naphthalenyl]propanamide.

N-Methyl-3-piperidino-*N*-[(1*R*)-1,2,3,4-tetrahydro-1-naphthalenyl]propanamide was made by the method of Example 134. ^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (m, 2H), 1.61 (m, 4H), 1.72-2.11 (m, 4H), 2.46 (m, 4H), 2.55-2.90 (m, 7H), 3.66 (m, 1H), 5.07 (m, 1H), 5.94 (m, 1H), 6.99-7.20 (m, 3H), 7.32 (m, 1H). m/s $(M+1)^+$= 301.

Example 136

Following conventional procedures well known in the pharmaceutical art the following representative pharmaceutical dosage forms containing a compound of formula I can be prepared:

(a)	Tablet	mg/tablet
	Compound of Formula I	50.0
	Mannitol, USP	223.75
	Croscarmellose sodium	60
	Maize starch	15.0
	Hydroxypropylmethylcellulose (HPMC), USP	2.25
	Magnesium stearate	3.0

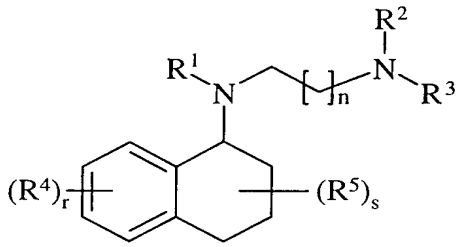
(b)	Capsule	mg/capsule
	Compound of Formula I	10.0
	Mannitol, USP	488.5
	Croscarmellose sodium	15.0
	Magnesium stearate	1.5

(c) Injection

For intravenous administration, a compound of Formula I is dissolved in an isotonic sterile solution (5 mg/mL).

CLAIMS

1. Any compound according to formula I:



I

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and phenylC_{2-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, phenylsulphonyl, 1-(1,2,3,4-tetrahydronaphthyl), a group of the formula IA:

$$—(CH_2)_p—A$$

IA

wherein A is halo, nitro, hydroxy, C_{1-6}alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl or *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, and p is an integer selected from the range 2 to 6, and a group of the formula IB:

$$—(CR^6R^7)_q—B$$

IB

wherein R^6 and R^7 are independently selected from hydrogen and C_{1-3}alkyl, and B is aryl, a carbon linked heteroaryl, a carbon-linked heterocyclyl, C_{3-12}cycloalkyl or C_{3-12}cycloalkyl fused to a benzene ring; q is an integer selected from the range 0 to 6; and wherein said aryl, heteroaryl or heterocyclyl may be optionally substituted on a ring carbon with one or more M groups where M at each occurrence is independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylSO_a where a is an integer selected from 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and

phenylC_{1-6}alkyl; and a heterocyclyl or a heteroaryl ring having an -NH- group may be optionally substituted on this nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl or phenylC_{1-6}alkyl, or

R^2 and R^3 together with the nitrogen atom to which they are attached form a heterocyclyl or heteroaryl ring, where said heterocyclyl or heteroaryl ring may have an -NH- group that may be substituted on the nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl or C_{1-6}alkylsulphonyl, said heterocyclyl or heteroaryl ring may have an -O- group, said heterocyclyl or heteroaryl ring may be optionally substituted with an ortho-fused aryl moiety, and wherein any aforesaid heterocyclyl, heteroaryl ring or aryl moiety may be optionally substituted on a ring carbon with one or more R^9 groups selected from M as heretofore defined,

r is 4 and R^4 at each occurrence is independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, cyano, nitro and C_{2-6}alkenyl;

s is 7 and R^5 at each occurrence is independently selected from hydrogen and C_{1-6}alkyl, and

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof;

provided that said compound of formula I is not *N*,*N*-diethyl-*N'*-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,2-ethanediamine, *N*-propyl-*N'*-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)-1,2-ethanediamine, *N*-propyl-*N'*-(1,2,3,4-tetrahydro-7-methoxy-1-naphthalenyl)-1,2-ethanediamine, *N*-propyl-*N'*-(1,2,3,4-tetrahydro-8-methoxy-1-naphthalenyl)-1,2-ethanediamine or *N*-propyl-*N'*-(1,2,3,4-tetrahydro-5,8-dimethoxy-1-naphthalenyl)-1,2-ethanediamine.

2. Any compound according to Claim 1,

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, phenylsulphonyl, 1-(1,2,3,4-tetrahydronaphthyl), and a group of the formula IB:

$$—(CR^6R^7)_q—B$$

IB

wherein R^6 and R^7 are independently selected from hydrogen and C_{1-3}alkyl, and B is aryl, a carbon linked heteroaryl, a carbon-linked heterocyclyl, C_{3-12}cycloalkyl or C_{3-12}cycloalkyl fused to a benzene ring; q is an integer selected from the range 0 to 6; and wherein said aryl, heteroaryl or heterocyclyl may be optionally substituted on a ring carbon with one or more groups independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, amino, C_{1-6}alkyl and C_{1-6}alkoxy, or

R^2 and R^3 together with the nitrogen atom to which they are attached form a heterocyclyl ring, where said heterocyclyl ring may have an -NH- group that may be substituted on the nitrogen with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl or C_{1-6}alkylsulphonyl, said heterocyclyl ring may have an -O- group, said heterocyclyl ring may be optionally substituted with an ortho-fused aryl moiety, and wherein any aforesaid heterocyclyl, heteroaryl ring or aryl moiety may be optionally substituted on a ring carbon with one or more groups independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, amino, C_{1-6}alkyl and C_{1-6}alkoxy, ,

r is 4 and R^4 at each occurrence is independently selected from hydrogen, halo, C_{1-6}alkyl;

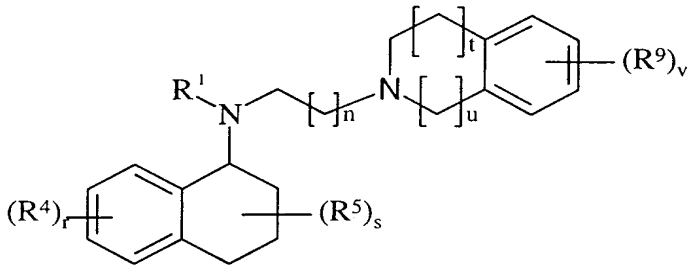
s is 7 and R^5 at each occurrence is hydrogen, and

n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof;

provided that said compound according to Claim 1 is not *N*,*N*-diethyl-*N'*-(1,2,3,4-tetrahydro-1-naphthalenyl)-1,2-ethanediamine, *N*-propyl-*N'*-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)-1,2-ethanediamine, *N*-propyl-*N'*-(1,2,3,4-tetrahydro-7-methoxy-1-naphthalenyl)-1,2-ethanediamine, *N*-propyl-*N'*-(1,2,3,4-tetrahydro-8-methoxy-1-naphthalenyl)-1,2-ethanediamine or *N*-propyl-*N'*-(1,2,3,4-tetrahydro-5,8-dimethoxy-1-naphthalenyl)-1,2-ethanediamine.

3. A compound according to Claim 1, of formula XIX



XIX

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and phenylC_{2-6}alkyl, and

v is 4 and R^9 is independently selected at each occurrence from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylSO_a where a is an integer selected from 0, 1 or 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl and phenylC_{1-6}alkyl;

r is 4 and R^4 at each occurrence is independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, cyano, nitro and C_{2-6}alkenyl;

s is 7 and R^5 at each occurrence is independently selected from hydrogen and C_{1-6}alkyl, and

n is 1 or 2, t is 0, 1 or 2, and u is 0 or 1;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

4. A compound according to Claim 1, selected from:

N^1,*N*^{1}-diisopropyl-*N*^{2}-methyl-*N*^{2}-1,2,3,4-tetrahydro-1-naphthalenyl]-1,2-ethanediamine;

N-[2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethyl]-*N*-methyl-*N*-[(1*S*)-1,2,3,4-tetrahydronaphthalen-1-yl]amine;

(1*R*)-*N*-methyl-*N*-(2-piperidinoethyl)-1,2,3,4-tetrahydronaphthalen-1-amine;

N^1-benzyl-*N*^{1}-methyl-*N*^{2}-[(1*S*)-1,2,3,4-tetrahydronaphthalen-1-yl]ethane-1,2-diamine;

N-[2-[3,4-dihydroisoquinolin-2(1*H*)-yl]ethyl]-*N*-methyl-*N*-[(1*R*)-1,2,3,4-

tetrahydronaphthalen-1-yl]amine;

N^1,N^1-dimethyl-N^2-methyl-N^2-1,2,3,4-tetrahydro-1-naphthalenyl]-1,2-ethanediamine;

N-(2-piperidinoethyl)-5,8-dimethyl-1,2,3,4-tetrahydronaphthalen-1-amine;

(1*S*)-*N*-[2-(1-azepanyl)ethyl]-1,2,3,4-tetrahydro-1-naphthalenamine;

(1*S*)-*N*-methyl-*N*-(2-piperidinoethyl)-1,2,3,4-tetrahydronaphthalen-1-amine;

N^1,N^2-dimethyl-N^1-phenethyl-N^2-[(1*S*)-1,2,3,4-tetrahydronaphthalen-1-yl]ethane-1,2-diamine;

N^1,N^2-dimethyl-N^1-phenethyl-N^2-[(1*R*)-1,2,3,4-tetrahydronaphthalen-1-yl]ethane-1,2-diamine;

N-methyl-*N*-(2-pyrrolidinoethyl)-(1S)-1,2,3,4-tetrahydro-1-naphthalenamine, and

N^1,N^1-diethyl-N^2-methyl-N^2-1,2,3,4-tetrahydro-1-naphthalenyl-1,2-ethanediamine.

5. A pharmaceutical composition comprising as an active ingredient an effective amount of a compound according to any of Claims 1 to 3, together with a pharmaceutically-acceptable carrier.

6. Use of a pharmaceutical composition according to Claim 5, for the therapy or treatment of stroke, head trauma, transient cerebral ischaemic attack, Alzheimer's disease, Parkinson's disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis or AIDS-related dementia.

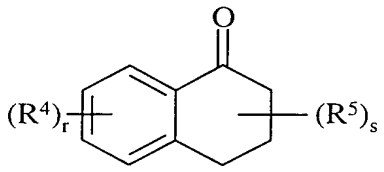
7. A method for treating or preventing neurological diseases by inhibition of the [^{3}H]-emopamil binding site, comprising administering to a mammal an effective amount of a compound according to any of Claims 1 to 3.

8. Use of a compound according to any of Claims 1 to 3, for preparation of a therapeutic agent or prophylactic agent for diseases treatable by inhibition of the [^{3}H]-emopamil binding site.

9. A method for treating or preventing diseases treatable by inhibition of the [^{3}H]-emopamil binding site, comprising administering to a mammal an effective amount of a compound according to any of Claims 1 to 3.

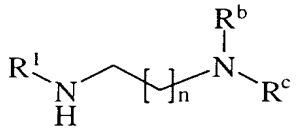
10. A process for preparing compounds of formula I wherein R^1, R^2, R^3, R^4, R^5 and n, are, as defined in Claim 1, which process comprises:

a) reacting a ketone of formula II:



II

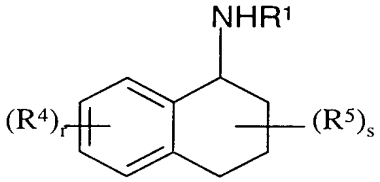
with an amine of formula III:



III;

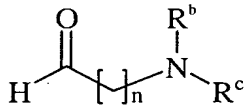
wherein: when R^2 or R^3 of a compound of formula I is hydrogen R^b and R^c are suitable amino protecting groups as defined hereafter; or when R^2 or R^3 of a compound of formula I is not hydrogen R^b and R^c are R^2 and R^3 respectively; or

b) reacting an amine of formula IV:



IV

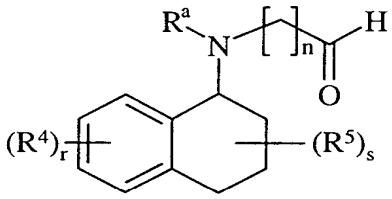
with an aldehyde of formula V:



V

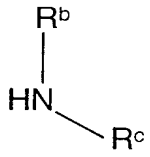
wherein R^b and R^c are as defined above; or

c) reacting an aldehyde of formula VI:



VI

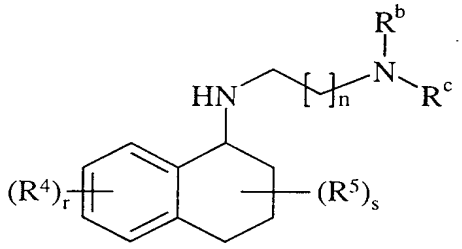
with an amine of formula:



VII

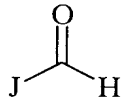
wherein: when R^1 of a compound of formula I is hydrogen R^a is suitable amino protecting group as defined hereafter; or when R^1 of a compound of formula I is not hydrogen R^a is R^1; or

d) if R^1 is C_{1-6}alkyl or phenylC_{2-6}alkyl, reacting a compound of formula VIII:



VIII

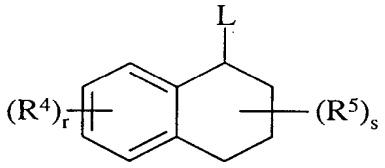
wherein R^b and R^c are as defined above, with a compound of formula IX;



IX

wherein J is hydrogen, C_{1-5}alkyl, or phenylC_{1-5}alkyl; or

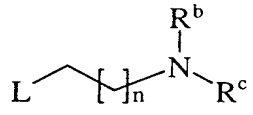
e) reacting a compound of formula X:



X

wherein L is a suitable displaceable group, with an amine of formula III; or

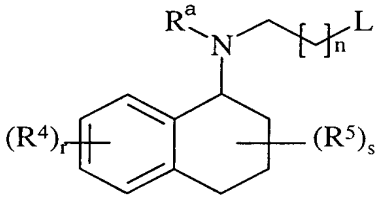
f) reacting an amine of formula IV with a compound of formula XI:



XI

wherein L is a suitable displaceable group and R^b and R^c are as defined above; or

g) reacting a compound of formula XII:



XII

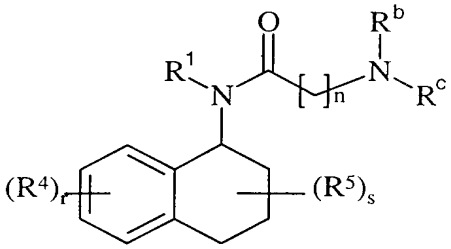
wherein L is a suitable displaceable group, with an amine of formula VII; or

h) if R^1 is not hydrogen, reacting a compound of formula VIII with a compound of formula XIII:

$$R^1\text{-}L \qquad \text{XIII}$$

wherein L is a suitable displaceable group; or

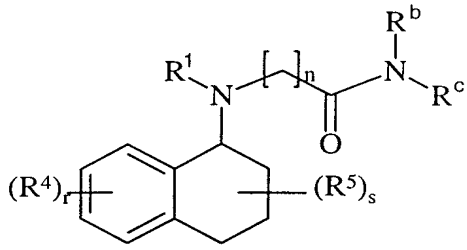
i) reducing a compound of formula XIV:



XIV

or

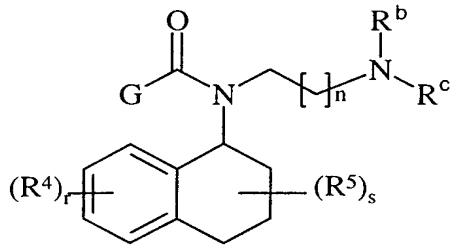
j) reducing a compound of formula XV:



XV

or

k) reducing a compound of formula XVI:



XVI

wherein:

for e), f), g) and h) L is a halogeno or sulphonyloxy group, such as chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy;

for k), G is C_{1-6}alkoxy, such as methoxy or ethoxy;

and thereafter if necessary:

i) converting a compound of the formula I into another compound of the formula I;

ii) removing any protecting groups; or

iii) forming a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or carbamate.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 99/04167

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D217/04 A61K31/472 A61K31/445 C07D295/13 C07D333/58
C07C211/42 A61K31/495 C07D211/58 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K C07C A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PERRONE R ET AL: "8-Methoxy- and p-dimethoxy-1-aminoethylheterotetralins: synthesis and DA, 5-HT receptor affinities" FARMACO (FRMCE8);1992; VOL.47 (10); PP.1285-91, XP000872444 Univ. Bari;Dip. Farm. Chim.; Bari; 70126; Italy (IT) the whole document ---	1-10
A	PERRONE R ET AL: "Synthesis and dopamine receptor affinities of 1-aminoethylheterotetralins" EUR. J. MED. CHEM. (EJMCA5,02235234);1991; VOL.26 (9); PP.869-74, XP000872480 Univ. Stud. Bari;Fac. Farm.; Bari; 70126; Italy (IT) the whole document ---	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 February 2000	10.03.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 99/04167

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 55677 A (HAMPRECHT DIETER WOLFGANG ;JARVEST RICHARD LEWIS (GB); MCNAIR DAVI) 4 November 1999 (1999-11-04) see compound examples 48,51,53	1,2,5
P,A	WO 99 38863 A (ZENECA LTD ;WARAWA EDWARD JOHN (US)) 5 August 1999 (1999-08-05) the whole document	1-10
P,A	WO 99 32461 A (ZENECA LTD ;KEITH RICHARD ALAN (US); SIMPSON THOMAS RICHARD (US);) 1 July 1999 (1999-07-01)	1-10

INTERNATIONAL SEARCH REPORT

Inte ..ational application No.
PCT/GB 99/04167

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7,9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/GB 99/04167

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9955677 A	04-11-1999	NONE	
WO 9938863 A	05-08-1999	AU 2289099 A	16-08-1999
WO 9932461 A	01-07-1999	AU 1571499 A	12-07-1999